

***United States Court of Appeals
for the
District of Columbia Circuit***



**TRANSCRIPT OF
RECORD**

089

JOINT APPENDIX

IN THE
United States Court of Appeals
FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 21,309

COMMISSIONER OF PATENTS, APPELLANT,

v.

WALTER SCHINDLER ET AL, APPELLEE

APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

United States Court of Appeals
for the District of Columbia Circuit

FILED NOV 30 1967

Nathan J. Parsons
CLERK

PART I

PART I
JOINT APPENDIX

United States Court of Appeals
DISTRICT OF COLUMBIA

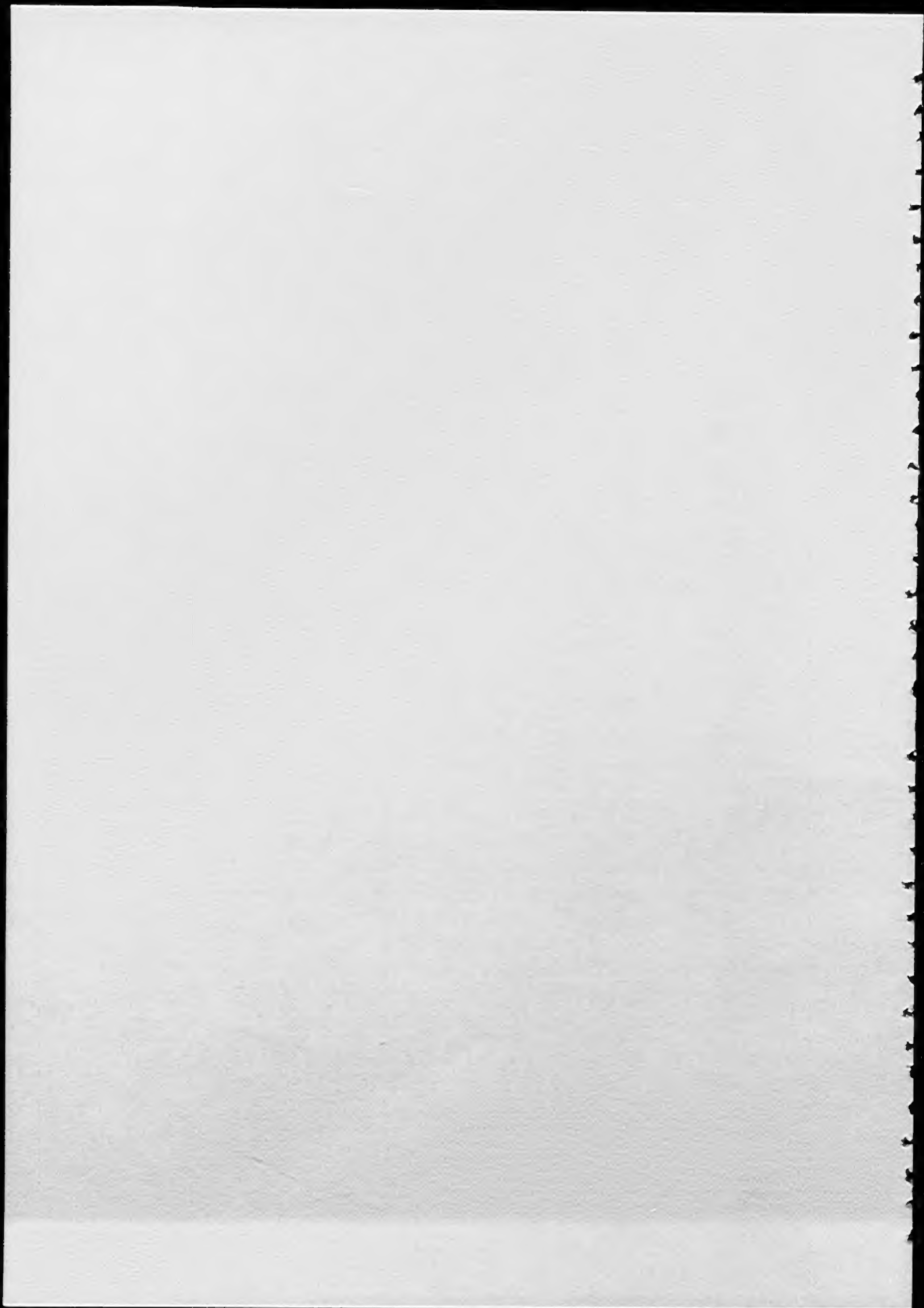
WALTER SCHINDLER and HENRI DIETRICH,
Plaintiffs-Appellants,

v.

COMMISSIONER OF PATENTS,
Defendant-Appellee.

APPEAL No. 19706

ON APPEAL FROM A JUDGMENT OF THE UNITED STATES
DISTRICT COURT FOR THE DISTRICT OF COLUMBIA



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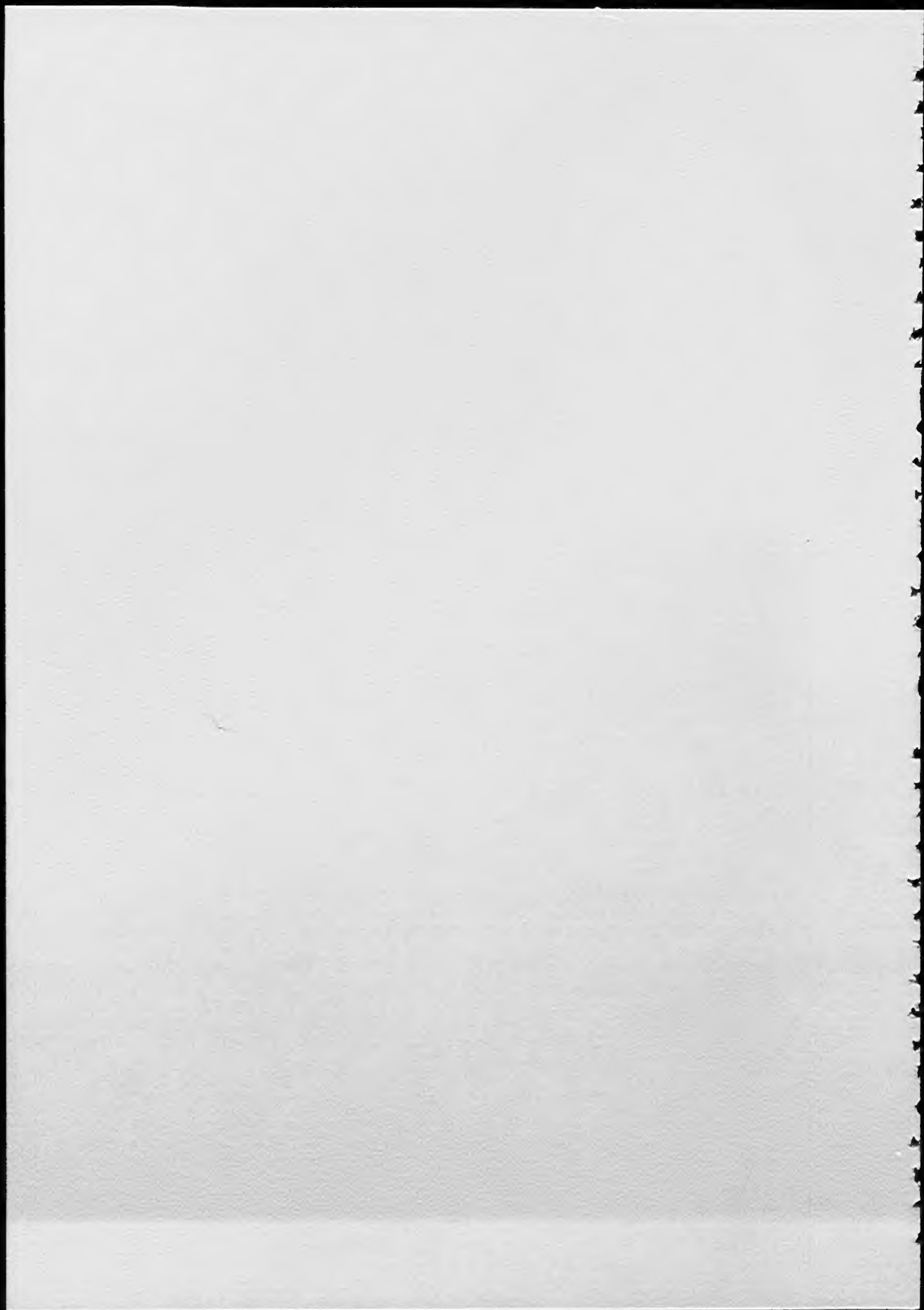
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Relevant Docket Entries.

CIVIL DOCKET UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

<i>Date</i>	<i>Proceedings</i>
1963	Deposit for cost by
Dec. 24	Complaint, appearance filed
Dec. 24	Summons, copies (3) and copies (3) of Complaint issued Ser 12-30-63 AG ser 1-2-64 U. S. Atty. ser 12-24-63
1964	
Feb 11	Answer of defendant to complaint, c/m 2-10-64 Appearance of C. W. Moore filed
Feb 11	Calendared (N) AC/N
1965	
Feb. 16	Hearing begun & concluded; taken under advisement; counsel to submit briefs, proposed findings of fact, conclusions of law & order. (Rep. Jack Maher) Jackson, J.
June 23	Transcript of proceedings—Feb. 16, 1965—pages 1 to 153, incl. (Rep. Jack Maher) (Court's copy) filed
June 23	Pre-trial brief of plaintiffs; c/s 2/12/65. filed
June 23	Post trial brief of plaintiffs. filed
June 23	Post trial brief of defendant; c/m 5/6/65. filed
June 23	Memorandum opinion, findings of fact and conclusions of law, finding in favor of defendant and dismissing complaint. (N) Jackson, J.
June 23	Judgment in favor of defendant and dismissing complaint; costs assessed against plaintiffs. (N) Jackson, J.

Complaint (Letters Patent).

1. The jurisdiction of this Court arises under Section 145 of the Patent Statute, Title 35 U. S. Code.

2. The plaintiff, Walter Schindler, is a citizen of the Swiss Confederation and a resident of Riehen near Basle, Switzerland.

3. The plaintiff, Henri Dietrich, is a citizen of the Swiss Confederation and a resident of Birsfelden near Basle, Switzerland.

4. On December 4, 1959, the plaintiffs filed in the United States Patent Office an application for U. S. Letters Patent entitled "New N-Heterocyclic Compounds", which application was assigned Serial No. 857,274.

5. The said application, Serial No. 857,274, was duly examined by the Primary Examiner who finally rejected all the claims thereof:

a. The claims were rejected as being unduly multiplied. Claim 3 was rejected solely on this ground.

b. Claim 1 was rejected as being drawn to a Markush group which lacks adequate support in the disclosure as filed, and as being based on new matter.

c. Claims 1, 2, 4, 6 and 8 to 13 were rejected as unpatentable over

Schindler et al 2,813,857

alone or in view of

Australian Patent 215,335.

Complaint (Letters Patent).

d. Claims 1, 7 and 17 were rejected as unpatentable over
Austrian Patent 200.578

alone or in view of

Australian Patent 215,335.

e. Claims 1 and 16 were rejected as not being patentably
distinct from claim 16 of application Serial No. 822,185
alone or in view of

Australian Patent 215,335.

6. An appeal from the final rejection by the Primary
Examiner was duly taken to the Board of Appeals of the
United States Patent Office.

7. The Board of Appeals, in a decision dated October
25, 1963, affirmed the Primary Examiner's rejection, and
refused to allow the claims of the said application, Serial
No. 857,274, or any of them, for the reasons set forth in
their said decision of October 25, 1963.

8. The decisions of the Primary Examiner and of the
Board of Appeals are erroneous in fact and in law.

9. The aforesaid claims of the said application, Serial
No. 857,274, duly recite invention and plaintiffs are entitled
to the allowance of such claims and to a patent granted
thereon.

10. There are no opposing or adverse parties.

11. Profert is hereby made of certified copies of the
said application and decisions.

Complaint (Letters Patent).

WHEREFORE, the plaintiffs pray that this Honorable Court adjudge and decree that the plaintiffs are entitled, according to law, to receive United States Letters Patent for the aforesaid invention, as specified in said claims or for any part thereof as from the facts in the case may appear; and the plaintiffs further pray that this Honorable Court authorize the Commissioner of Patents to issue such Letters Patent on the filing in the Patent office of a copy of a favorable adjudication to such effect, and upon other compliance with the requirements of law.

WENDEROTH, LIND & PONACK
and A. Ponack
A. PONACK
A member of the firm
Attorneys for Plaintiffs
1343 H Street, N. W.
Washington 5, D. C.

December 24, 1963.

Answer to Complaint.

TO THE HONORABLE THE JUDGES OF THE UNITED STATES
DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

1, 2, 3, 4, 5, 6, 7. The defendant admits the allegations of paragraphs 1, 2, 3, 4, 5, 6 and 7 of the complaint.

8, 9, 10. The defendant denies the allegations of paragraphs 8, 9 and 10 of the complaint.

11. The defendant admits the allegations of paragraph 11 of the complaint.

FURTHER ANSWERING, the defendant asserts that only claims 4, 6, 7, 8, 11, 16 and 17 of plaintiffs' application for patent, Serial No. 857,274, are properly before this Court for review, since those claims alone were involved in the decision on patentability of the Board of Appeals in plaintiffs' application; and that plaintiffs are not entitled to a patent containing any of those claims or any of claims 3, 9, 10, 12 and 13 of the same application, in view of the patents cited and the application identified, and on the basis of the reasons given, relative thereto, in the Examiner's Answer, the Examiner's Answer on Remand, and the decision of the Board of Appeals in the application. Proffert hereby is made of copies of the said answers, decision, identified application, and cited patents.

Respectfully submitted,

C. W. MOORE
Solicitor, United States Patent Office
Attorney for Defendant

February 10, 1964

I hereby certify that two copies of the foregoing ANSWER TO COMPLAINT were mailed today to Wenderoth, Lind & Ponack, 1343 H Street, N. W., Washington 5, D. C., attorneys for the plaintiffs.

C. W. MOORE
Solicitor

Relevant Testimony.**(24) TESTIMONY OF DR. DANIEL A. PRINS**

Direct Examination by Mr. Ponack:

Q. Dr. Prins, what is your full name? A. Daniel A. Prins, P-r-i-n-s.

Q. And your address? A. 18 Birkenstrasse in Oberwil, near Basle, Switzerland.

Q. Would you please briefly outline your education? A. My education starts at the Technical High School or University at Delft, Netherlands, and it was continued at the Federal Institute of Technology in Zurich, Switzerland, and it culminated in a Doctorate Thesis at the University of Basle in Switzerland.

Q. So you have what degrees? A. I am a Chemical Engineer and a Ph.D.

Q. Are you a member of any professional or learned societies? A. Yes, sir.

I am a member of the American Chemical Society, of (25) the Chemical Society of London, of the Royal Dutch Chemical Society and of the Swiss Chemical Society.

The Court: Are you an American?

The Witness: I have lived here, your Honor.

The Court: You talk like an American, and when you said you were a member of the American Chemical Society I was wondering.

By Mr. Ponack:

Q. Are you the author of any publications? A. Yes, sir, indeed. About thirty-five.

Q. And, generally, what do these refer to? A. Mostly natural products of the nature of alkaloids, steroids and also with carbohydrates.

Testimony of Dr. Daniel A. Prins—Direct.

Q. Have you ever been associated with any college or university? A. Yes, sir, I have. I have been Assistant Professor at the University of Montreal in Montreal, Canada, and I have had similar positions with the Frank E. Bunts Educational Institute in Cleveland, Ohio.

The Court: When you were in Montreal were the classes conducted in French or in English?

The Witness: I had no classes to conduct because the institute was so new that there were no students, your Honor.

(26) The Court: I see.

By Mr. Ponack:

Q. Have you had occasion to do any research work in the field of iminodibenzyls? A. Yes, sir, I have.

Q. Will you outline this work, please? A. In about 1957, when I joined the company, I was assigned to the iminodibenzyl field, where I first worked synthetically in the laboratory using compounds and developing processes besides continuing some natural product work. Later on my assignment in this field was more of an administrative nature. That is what I am doing now as a Group Leader.

The Court: Where are you working now?

The Witness: At the same company and in the same area of work.

By Mr. Ponack:

Q. Do you mean Geigy, Basle? A. Geigy, Basle.

Q. The assignee of the application? A. That is right.

Q. Will you indicate what is involved in your current work? A. As I briefly intimated, I am now a Group Leader leading a group of chemists preparing compounds in the

Testimony of Dr. Daniel A. Prins—Direct.

(27) iminodibenzyl field. I direct or influence their research projects in formulating them and evaluating chemical as well as biological data that comes out of pharmacological testing.

The Court: I think Dr. Prins is sufficiently qualified, Mr. Ponack.

Mr. Ponack: Thank you, your Honor.

By Mr. Ponack:

Q. Are you familiar with the Schindler et al. application involved in this suit? A. Yes, sir.

Q. What is the compound of Claim 8? A. The compound of Claim 8 is 3-dimethylamino-propylmonochloro-iminodibenzyl.

The Court: You haven't attempted to shorten that, have you, by giving it a tradename? Is this in use?

Mr. Ponack: It is being tested, your Honor.

The Court: I see.

Mr. Ponack: It is in clinical testing.

The Court: After it is tested and, if successful, you will give it a short name?

Mr. Ponack: Undoubtedly they will, your Honor.

By Mr. Ponack:

Q. You know, of course, on what the claim is rejected? (28) A. On the two patents, as I understand, namely United States patent 2,813,857 and on the Australian patent, the number of which is already in the record.

Q. I hand you a copy of the Schindler et al. patent 2,813,857. Will you please tell the Court what this patent teaches? A. This patent teaches dichloro-iminodibenzyl

Testimony of Dr. Daniel A. Prins—Direct.

compounds having different tails, as exemplified in Example 1 and Example 2.

Q. What is the characteristic feature of the nucleus, the iminodibenzyl nucleus? A. This type of iminodibenzyl is referred to as a symmetrically substituted iminodibenzyl.

The Court: You are talking too rapidly.

The Witness: Excuse me, sir. As a dihalo iminodibenzyl—

By Mr. Ponack:

Q. Dr. Prins, it might help if you would use the chart which you have prepared in connection with this patent.

The Court: Furnish the witness with a pointer, please, Mr. Marshal.

[The witness stepped down to a chart mounted on an easel.]

By Mr. Ponack:

(29) Q. What does this chart show? A. This chart shows the synthesis of dichloro-iminodibenzyl. This is shown down here (indicating), and the final product thereof (indicating).

Q. Will you kindly go through this for the Judge's edification and explain each step, just what happens, and the significance of it? A. The patent discloses the cyclization of this (indicating) dichloro compound to dichloro-iminodibenzyl and the affixing of the tail.

The process that is used to arrive at this dichloro-iminodibenzyl is through this intermediate (indicating) and previously through that one (indicating). It starts from two halves. These molecules are called substituted toluenes. This (indicating) is the toluene part of the

Testimony of Dr. Daniel A. Prins—Direct.

molecule. In fact, it starts from two molecules of ortho-nitro toluene. This (indicating) is one molecule and this is the other one. And these molecules are caused to react under appropriate conditions and there results this compound here (indicating) which has a long chemical name, but maybe the picture is more illustrative to Your Honor.

Essentially what happens is that the two methyl groups are reacted in such a way as to form a bond between each other and build this ethylene bridge $\text{CH}_2\text{-CH}_2$ between the (30) two.

The Court: These are Examples shown in the patent, are they not?

The Witness: This is not shown in the Schindler et al. patent, your Honor.

The Court: I see that in Example 2 except it has a tail.

The Witness: Example 2 has the final product, your Honor. Example 2 is made from this one (indicating).

By Mr. Ponack:

Q. In other words, you are giving the synthesis? A. The full synthesis.

Q. Leading up to where the patent starts? A. That is right, the patent starts here (indicating).

Q. Continue. A. In other words, from this product, which is essential in getting the next intermediate, this is a dinitro compound which is reduced, as indicated here (indicating) by the word "Reduction" in the second step, to another intermediate, which is a diimino compound. This diimino compound is already exemplified in the Schindler et al. patent and used here as a starting material. This diimino compound is now caused to react in the process of what we (31) cyclization, because of the

Testimony of Dr. Daniel A. Prins—Direct.

effect of closing of the cycle to the 3,7-dichloro-iminodibenzyl.

This is the intermediate we need for putting our tail on, which is done in a separate 4th step, to introduce the final product of the Schindler et al., patent, being 3-dimethylamino-propyl-3,7-dichloro-iminodibenzyl, which then is reached in a total of four steps.

Q. Will you, for the record, explain to his Honor the difference between the 3,7, which you have just made, so to speak, and the 3-chloro compound of claim 8 involved in this suit? A. This, as I intimated before, is different from the 3-chloro compound in the fact that it has to begin with two chlorine atoms. The claim 8 compound has only one. This compound has not only two chlorine atoms, it has those two chlorine atoms symmetrically distributed with respect to the iminodibenzyl nucleus. The claim 8 compound doesn't have that feature.

Q. And where is the chlorine atom? Is there any specific location? A. The location in the Schindler et al. compound is specific in that it is specifically at 3 and 7; and the claim 8 compound is also specific, because it is in the 3 position.

(32) Mr. Ponack: If your Honor please, I have had Dr. Prins reduce his chart to a small form here so that we can offer it in evidence.

By Mr. Ponack:

Q. Dr. Prins, would you check this against what is on the easel and tell us if there are any essential differences? A. This (indicating) on the sheet is called "Key Intermediate I".

The Court: Is that a reproduction on a small scale of what you have on the easel?

Testimony of Dr. Daniel A. Prins—Direct.

please bear with us. This is a rather long and complex synthesis.

The Court: I understand.

The Witness: The actual synthesis—

The Court: Now is this the synthesis used in the product of the application?

The Witness: It was used, your Honor.

The Court: All right.

The Witness: The situation at the time that Dr. Schindler wanted to prepare this 3-monochloro compound was such that it was necessary to start out to build up by a process very analogous to the one I have just shown. The unsubstituted iminodibenzyl, instead of having chlorines in we have nothing in. The rest is the same. We have two halves which we condense to a first intermediate, which is reduced to a second intermediate which is cyclized to unsubstituted iminodibenzyl.

The problem of putting the chlorine atom in at the point that we wanted it, namely at this point 3 (indicating), was achieved by reacting this unsubstituted iminodibenzyl first with acetyl chloride in order to protect the 5 position, which is a rather reactive one, and we didn't want the (36) chlorine in there.

Q. What is acetyl chloride and what does it introduce?

A. It introduces the acetyl group on the nitrogen of the iminodibenzyl.

Q. So that the chlorine cannot go there? A. Therefore, this nitrogen atom is now removed from attack. It is protected, as we call it.

Five-acetyl-iminodibenzyl was put through a process which we call the Friedel-Crafts process. This process has the effect of introducing—acetyl chloride was used here—

Testimony of Dr. Daniel A. Prins—Direct.

the acetyl group into the molecule. It was found that the attachment of this acetyl group happened to occur in the 3 position.

Q. Was this fortuitous? A. It could not have been expected.

Q. I see. A. We were very happy when we found it did that.

Now there is a standard chemical process which can convert such substituents into other ones. This one here is called the Schmidt process. It uses hydrozoic acid, which is a rather nice chemical. It converts this group to an acetyl-imino group, nitrogen being taken off of the reagent being affixed between the acetyl group and the nucleus to give this so-called imino group. This derivative (37) can be partially changed in such a way as to eliminate one of the acetyl groups. This is called a hydrolysis, and it is called a partial hydrolysis because only one of the two acetyl groups is removed and it is removed on the nitrogen atom which we now have in the 3 position; and it produces a 3-amino-5-acetyl-iminodibenzyl.

This compound can be reacted or be put through a series of reactions, the result of which is to exchange this amino group for a chlorine in this instance. That is done by the Sandmeyer reaction, as is well known in diazonium chemistry. The diazonium compound is reacted with a halide, in this case copper chloride. The chlorine atom in this reactant is affixed instead of the nitrogenous group we have here in the nucleus, and now we have for the first time what we wanted to have, namely chloro introduced in the 3 position of an iminodibenzyl group which still is protected on the 5 position nitrogen atom.

This acetyl group can be removed, again by hydrolysis, in this case more vigorous than previously, giving the 3-chloro-iminodibenzyl, which is the essential intermediate for making products of the type of the Claim 8 compound.

Testimony of Dr. Daniel A. Prins—Direct.

Because we need this with a reacted imino group in the 5 position to be able to affix the tail, which is symbolized here (indicating), the tail being the moiety Mr. (38) Ponack explained on the board, namely dimethyl aminopropyl. This last operation which occurs in the 11th step produces the Claim 8 Compound.

Q. If stepwise chlorination were possible, would you go through this series of steps? A. No, sir. We would be very happy if we had a short process.

In fact, realizing that this is a very costly and long-winded affair, we looked for shorter processes. Stepwise chlorination on chemical grounds did not appeal to us too much, but we thought we might vary the original synthesis used for the symmetrical compound in a way that would lead to asymmetrical compounds.

Q. Before you go on to that, would you please look at this before we leave it? Would you check this and state whether or not this is a duplicate of the large chart you just explained concerning the 11 steps of the synthesis? A. It is not an exact duplicate. It is an essential duplicate.

Mr. Ponack: Mr. Armore, have you any objection to our offering this (indicating)?

Mr. Armore: Does it correspond?

Mr. Ponack: Yes.

Mr. Armore: No objection.

(39) The Court: Mark it in evidence.

The Deputy Clerk: Plaintiffs' Exhibit Number 3 is marked in evidence.

(Plaintiffs' Exhibit No. 3 was received in evidence.)

By Mr. Ponack:

Q. Continue, Dr. Prins. A. If I may briefly summarize,

Testimony of Dr. Daniel A. Prins—Direct.

we have seen in Chart Number 1 a symmetrical condensation containing chlorine.

In Chart 3 which was just offered in evidence we have seen a symmetrical condensation without chlorine. It was felt worthwhile trying having one partner unsubstituted and the other partner substituted, chlorine built in, and have those react the same way as in the other process, namely hooking up through the methyl groups to form again a dibenzyl which we hoped would be this one (indicating) having a chlorine atom here and a hydrogen atom here. However, that did not work at all. This compound—

Q. Excuse me. Was this work done by you or under your supervision? A. Yes, sir, I did this work myself.

Q. Go ahead. A. If these two reagents are caused to react under the conditions the other syntheses worked, it is not this (40) compound that is formed (indicating) and isolated, it is this one.

Q. What is "this one"? A. This is the symmetrically substituted dichloro compound. It was the only compound that could be isolated from the reaction mixture, a number of other compounds being formed, some of which are identified by functions, such as acids and bases, the large part being inseparable mixtures.

Q. Check this one (indicating) in the same way. Is this essentially what you have on the blackboard?

The Court: Is that a true and correct copy of what you have on that large chart?

The Witness: Yes, sir.

By Mr. Ponack:

Q. Is it a true and correct copy? A. Yes, sir.

Mr. Armorer: No objection, your Honor.

Testimony of Dr. Daniel A. Prins—Direct.

rings eight possibilities. We can leave out the disubstituted because they are not of interest here. We will concern ourselves with the monosubstituted, leave the Y out. We have here the possibility of 1, 2, 3 and 4 in the second Y. Y₁, as it (44) is called here can be hydrogen. That is specific. It can be halogen. Which halogen? There are four halogens. It can be alkyl, alkyl from 1 to 6 carbon atoms. A propyl group, your Honor, is an example of an alkyl group having 3 carbon atoms. This alkyl group that can be in place of Y can have 1 to 6 carbon atoms (indicating). That makes 4 possibilities, 6 possibilities. An alkoxy group, the alkyl of the alkoxy having 1 to 6 carbons, six possibilities. An aryl group. What is meant by an aryl group we don't know. It is absolutely unspecific.

Q. How many groups would be comprised, to your knowledge, in an aryl group? Would it be of the order of hundreds, thousands or hundreds of thousands? A. I would say at least one-thousand that I could remember.

As far as the nucleus is concerned then, we have 4 and 6, which is 10, and 6, which is 16, a thousand here (indicating) conservatively, which makes 1,016, plus another makes 2,032—I cannot calculate it, your Honor. It is a large number.

Q. And each one of those can be in permutation and combination with various A's or various R's; is that right? A. The number becomes more staggering.

This is with respect to the nucleus. The preparation (45) of any substituent Y other than hydrogen is not given in the patent.

Q. And was there any method of preparing such a compound known at that time? I think I have asked this once before, but since you have raised the point I would like to have the record show again was such a process known.

A. To make the unsubstituted, yes, but to make the monosubstituted, no.

Testimony of Dr. Daniel A. Prins—Cross.

Q. Dr. Prins, I hand you the chart prepared by the Solicitor which was handed to the Court at the beginning of the trial, and direct your attention to the summary there of what is shown in the generic disclosure of the Australian patent. Do you see any reference to alkoxy there?
A. No.

Q. For Y and Y₁? A. No.

Q. Do you see any reference aryl there for Y and Y₁?
A. No, sir.

Q. Do you see any reference to O aryl for Y and Y₁?
A. No, sir.

Q. Then this is an incomplete summary, is it not, of what this reference shows? A. I would say so.

Q. Please look at the reference and point out just where (46) it says O Alkyl? A. O Alkyl is in the reference.

Q. Where? A. No, it says lower alkoxy in the patent.

Q. Yes. Well, what is lower alkoxy, what does it mean?
A. It is O Alkyl.

Q. And where is there aryl? A. Just behind that in the patent.

Q. Do you mean in the next line? A. Yes.

Q. And where is O Aryl? A. Just after that as aryloxy.

Q. And aryloxy is what you mean when you write O Aryl, is that right? A. That is right.

Q. Do you see any teaching in the Australian patent which, to quote the decision of the Board of Appeals in this case, renders it obvious—this is the Board's words—renders it obvious to modify the dichloro compounds of the Schindler et al. patent? A. Modification, no, sir.

Mr. Ponack: Your witness, Mr. Armore.

Cross Examination by Mr. Armore:

(47) Q. Dr. Prins, I hand you defendant's exhibit 2 for identification. This is the chart concerning which you

Testimony of Dr. Daniel A. Prins—Cross.

have just testified. I direct your attention to column 1 of that chart which names a chemical compound under Claim 8 and gives the structural formula of that compound. Does this name and structural formula correspond accurately to the compound of Claim 8? A. Yes, sir.

Q. You have just testified concerning the Schindler et al. patent, which is shown in columns 2 and 3 of that chart. I direct your attention to the generic disclosure in column 2 of the chart, which is entitled "Generic Disclosure Imino-dibenzyl Derivatives" and gives the generic structural formula and the values for all the variables disclosed generically in the Schindler et al. patent. Does the subject matter in column 2 of the chart accurately correspond to the generic disclosure in the Schindler et al. patent? A. With respect to X it does. With respect to alkylene I think it is complete insofar as the patent specified 2 to 4 bridging members.

Q. Is there anything in column 2 that you consider inaccurate as representing the generic disclosure in Schindler et al.? A. Incomplete, I would say.

(48) Q. Incomplete in what respect? A. For example, with respect to alkylene the chart says "alkylene is an alkylene radical with 2-6 carbon atoms" whereas the patent says "and 2-4 bridging members."

Q. Yes. The 2-4 bridging members has been omitted. That is the principal difference you notice between what is shown in the chart and the patent; is that correct? A. With respect to the alkylene?

Q. Yes. A. Yes.

Q. Now with respect to the value of X, that is correct; is that right? A. "X is a halogen atom." X represents a halogen atom. We can take that to be the same thing.

Q. That corresponds to the Schindler disclosure? A. Yes.

Q. I direct your attention to the value of AM. Does what appears on the chart correspond to the values of AM

Testimony of Dr. Daniel A. Prins—Cross.

as shown in the Schindler et al. disclosure? A. Here you have the addition of "pyrrolidino or piperidino radical" in your chart.

Q. Do those additions correctly characterize the values of AM as disclosed in Schindler et al.? (49) A. Yes, sir.

Q. Is it true that the tail substituents in the iminodibenzyl compounds of Schindler et al. may be a heterocyclic nitrogen substituent, which may be either pyrrolidino or piperidino? A. May be heterocyclic mononitrogenous substances.

Q. Yes. And the nitrogen of these heterocyclic rings are attached to the iminonitrogen through the alkylene bridge, is that correct? A. That is correct.

Q. Does the compound disclosed or shown in column 3 of the defendant's chart entitled "Example 2" and giving the name of the compound and giving the structural formula correspond to the compound which is disclosed in Example 2 of the Schindler et al. patent? A. It does.

Q. Is it true that this compound distinguishes from the claimed compound only in having an additional or one additional chlorine atom which is positioned in the 7 position? A. Structurally it does.

The Court: It is time now for the usual morning recess, Mr. Marshal.

The Deputy Marshal: This Honorable Court stands (50) recessed until 11:30.

(Whereupon, at 11:15 a.m. the Court recessed as noted and reconvened at 11:35 a.m.)

The Court: You may continue your cross examination, Mr. Armore.

By Mr. Armore:

Q. Dr. Prins, you have testified concerning the Australian patent. I call your attention to column 4 of the

Testimony of Dr. Daniel A. Prins—Cross.

defendant's chart, concerning which you have already testified. With the exception of the fact that Y and Y₁ do not enumerate all of the possible substituents, would you agree that column 4 accurately represents the generic disclosure of the Australian patent? A. With respect to Y and Y₁, that is correct, and enumerating hydrogen, halogen and lower alkyl as appears in column 4.

With respect to A it is substantially correct.

The Court: Speak into the microphone, please, Dr. Prins.

The Witness: With respect to R, that is also essentially correct.

By Mr. Armore:

Q. Would it be correct to say that the classic compounds represented by the generic disclosure in the (51) Australian patent differs essentially or exclusively—I withdraw that question.

Would it be correct to state, that insofar as the main nucleus of the compound in the Australian patent is concerned, that this nucleus may be either unsubstituted, monosubstituted or disubstituted? A. That is correct except that the generic disclosure doesn't disclose a nucleus alone.

Q. Is it true that among the various possible substituents for the nucleus, the main nucleus of the iminodibenzyl compound shown in the Australian patent, may be halogens? A. According to the disclosure, yes.

Q. And do these halogens also include chlorine? A. They do.

Q. Is it true that essentially the main difference between the generic disclosure of the Australian patent and the generic disclosure in Schindler et al., aside from—

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The Court: Which are you talking about when you say the Schindler et al., the application or the patent?

Mr. Armore: The Schindler et al. patent.

The Court: All right.

By Mr. Armore:

Q. Aside from the substituents in the main nucleus, is (52) with respect to the tail substituent attached to the iminonitrogen through the alkylene group? A. If I get your question correctly, you are referring to the difference between the Schindler patent and the Australian with reference to the tail?

Q. That is correct. A. The difference lies in the piperazino moiety in the Australian and the mononitrogenous piperazine group in the Schindler et al.

Q. Since you are familiar with both the Schindler et al. and Australian patents, are you also familiar with the disclosures as to the pharmacological utility described and disclosed in those patents? A. I have read them.

Q. Do you agree that the Australian patent discloses, as among the pharmacological or pharmacodynamic properties, antiemetics, antihistaminics, spasmolytics and antiepileptics? A. That is in the Australian disclosure.

Q. As one familiar with the biological and pharmacological properties of these iminodibenzyl compounds, would you agree that usually sedatives are used as antiemetics, antiepileptics and antihistaminics and spasmolytics? A. I wonder whether this is within the field of my expertise?

(53) The Court: I was thinking that is more medical than it is chemical.

You needn't answer it.

The Witness: Thank you, your Honor.

Testimony of Dr. Daniel A. Prins—Cross.

By Mr. Armore:

Q. As an organic chemist, viewing the disclosures in the Schindler et al. and Australian patents, would the concept of a dichlorosubstituted nucleus corresponding to the monochlorosubstituted nucleus be an obvious chemical concept?

A. That depends on how you understand obvious. As an organic chemist, the structure means the synthesis of the symmetrical compound we have elaborated on this morning. And we have said that we did not know how to make the monosubstituted asymmetrical compound until we found a way to do it.

Q. Dr. Prins—I am sorry. Have you finished? A. Yes.

Q. Aside from the matter of preparation of the synthesis, in terms of concepts of compounds, would the two disclosures in the Schindler et al. patent and the Australian patent indicate to the organic chemist the concept of a dichloro compound corresponding to the monochloro compound of Schindler? (54) A. I don't know whether we understand each other correctly.

As an organic chemist, the suggestion would be linked through the synthesis. I do not know beyond that.

The Court: In other words, as a chemist, you would say it would not be obvious?

The Witness: To a chemist a compound is obvious when he can make it, not when he can think it, your Honor.

The Court: I know, but the thing is this: If you had the Schindler structural formula and the Australian structural formula, together with the disclosures in the specifications, would it be obvious then to do what was done in making the asymmetric substitute? Would you say, oh, sure, this is easy?

The Witness: One would think about it but one would run the reaction, which was done and found to be inadequate.

Testimony of Dr. Daniel A. Prins—Cross.

The Court: I see.

By Mr. Armore:

Q. Dr. Prins, I refer you to the chart which was demonstrated to the Court and which corresponds to plaintiffs' exhibit 2, which shows the preparation of the 3,7-dichloro shown in the Schindler et al. patent compound. Now with respect to the first step of coupling, would you achieve a (55) coupling reaction, if instead of using for this starting material on the left you used a non-chlorine orthonitro toluene instead of a chlorine? In other words, is it true that if you used a non-chlorine nitro toluene and chlorine nitro toluene you would couple to get a monochlor compound? A. That would be the expectation.

Q. Do you get that? A. No, sir.

Q. You do not get it? A. No, sir.

Mr. Ponack: Excuse me. We can't hear, Doctor, unless you move in a little. Thank you.

By Mr. Armore:

Q. Do you get a mixture of monochloro and dichloro compounds as a result of the coupling reaction? A. That is a possibility. I do not know for sure.

Q. You haven't—I am sorry. A. Because I haven't been able to resolve the mixture.

Q. Have you made efforts to resolve the mixture? A. Yes, sir.

Q. How many efforts? A. Hundreds of efforts. I have applied chromatographic techniques which are known to be good techniques in (56) separation of organic compounds of this type; and I have been able to isolate from those chromatographs only the symmetrically substituted dichloro compound to which you are pointing.

Q. Have you tried differential solubility methods? A. In recrystallization, yes. The components did not separate.

Testimony of Dr. Daniel A. Prins—Cross.

Q. But you have tried differential solubility methods?

A. That is right.

Q. Have you tried other chemical procedures? A. No, I was trying separation procedures.

Q. I would like to refer you to the Examiner's Answer on Remand, defendant's exhibit 1-E.

Mr. Armore: May the witness have a copy of that, your Honor?

The Court: He may use my copy if he wants to.

Mr. Armore: May he use your copy, your Honor, so I can retain mine for a moment?

The Court: Yes.

Mr. Armore: Thank you, your Honor.

By Mr. Armore:

Q. I refer you to page 2 of the Examiner's Answer on Remand, and I ask you to read the portion starting about one-third of the way down—

(57) The Court: Aloud or to himself?

Mr. Armore: Aloud.

The Court: All right.

By Mr. Armore:

Q. It starts "That is to say" near the end of the line about one-third of the way down. Do you see that? A. (Reading) "That is to say that it would be obvious to one of ordinary skill in the art desiring the monosubstituted iminodibenzyl to react ortho-nitro toluene with the substituted ortho-nitro toluene to form the desired intermediate. This reaction would proceed as follows:"—

Q. I will stop you at that point, Doctor. And then the reaction indicated is the reaction between ortho-nitro

Testimony of Dr. Daniel A. Prins—Cross.

toluene and 3-chloro ortho-nitro toluene as corresponding to the coupling reaction we have here; is that correct? A. Yes.

Q. Now do you disagree with this statement made by the Examiner?

Mr. Ponack: If your Honor please, I think the witness has answered this question several times.

The Court: Well, let him answer it again. It won't hurt. Of course, that is a question of obviousness, which is rather an intangible thing.

The Witness: He would hope to get the result (58) depicted on this page and he would try to make the experiment in the laboratory.

The Court: Would it be obvious for him to do it?

The Witness: The desire would be obvious, the intention, but the outcome would not be obvious.

The Court: I see.

By Mr. Armore:

Q. Dr. Prins, I refer you now to the Schindler et al. patent. Do you have a copy of that patent in front of you? A. Yes, sir.

The Court: By the way, that Austrian patent has nothing to do with this suit now, does it?

Mr. Armore: No, the Austrian patent is not now in the suit.

The Court: I notice it is in your exhibit.

Mr. Armore: Yes, your Honor, it is there.

Also, your Honor, may I point out that I added another exhibit G, which isn't actually in the record, but it was necessitated by the fact other claims appeared to remain in the suit. However, since the other claims are not in the suit, that additional exhibit is not to be considered.

Testimony of Dr. Daniel A. Prins—Cross.

The Court: It is not to be considered?

Mr. Armore: No, your Honor, it is of no interest.

(59) The Court: All right.

By Mr. Armore:

Q. I refer you to the Schindler et al. patent, column 1, starting at line 45. Would you please read from line 45 to line 50? A. In the first column, sir?

Q. The first column, line 45 to line 50. A. (Reading) "The new compounds are produced by reacting an iminodibenzyl substituted as defined, in the presence of acid binding agents with a reactive ester of an alcohol of the general formula:

"HO—alkylene—Am."

Q. Does this correspond precisely to the first method for preparing the compound of Claim 8? The Claim 8 disclosed in the application in suit. A. The last step in the synthesis.

Q. Are there any other steps in the synthesis disclosed in the application in suit? A. Of putting the tail on.

Q. Pardon. A. The tail affixing operation.

Q. What is the starting material indicated in the method for preparing the claimed compound in the application in suit? What are the starting materials indicated? (60) A. The starting materials are the unsymmetrically substituted iminodibenzyl and tail affixing operations, a number of which I do not recall offhand.

Q. Do you have a copy of the application in suit? A. I have one in my brief case.

Am I allowed to get it, your Honor?

The Court: You may step down and get it.

Testimony of Dr. Daniel A. Prins—Cross.

By Mr. Armore:

Q. Dr. Prins, I refer you to page 2 of the application in suit starting in the middle of the page, the last paragraph. A. Yes.

Q. And I ask you to read that paragraph to yourself. A. Yes, sir.

Q. Would it be true to say that the method disclosed in that paragraph you have just read corresponds exactly and identically to the method disclosed in the Schindler et al. patent, the only difference being that in the application in suit the starting material is a monochloro iminodibenzyl, and the starting material in the Schindler et al. patent is a dichloro iminodibenzyl? A. Yes, sir.

Q. Is it true that the starting materials which are disclosed in all the other methods in the application in suit also start with an iminodibenzyl substituted compound? (61) A. All the others? Would you please repeat this?

Q. All the other methods for preparing the compound of Claim 8 in the application in suit all start with substituted iminodibenzyl compounds? A. That is correct.

Q. Which are monochloro substituted? A. That is correct.

Q. Would you recognize that one could correspondingly prepare the dichloro compound by using a dichloro iminodibenzyl starting material instead of a monochloro iminodibenzyl starting material in the methods disclosed in the present application? A. Yes, sir.

Q. Are you familiar with the method for preparing the compounds disclosed in the Australian patent? A. I can refresh my memory from this copy?

Q. Yes, go right ahead. A. Thank you. I am.

Q. You are aware that the Australian patent discloses seven methods for preparing the compound? A. That is correct.

Testimony of Dr. Daniel A. Prins—Re-direct.

Q. I refer you to the first method on the second page of the Australian specification in column 1. Does this (62) method correspond fully and completely to the method disclosed in Schindler and the first method disclosed in the present application in suit? A. The method as spelled out, yes.

Q. I refer you to the second method in the Australian patent. Does this method correspond to the third method disclosed in the application in suit? A. Yes, sir, it does in principle.

Q. And, finally, I refer you to the seventh method in the Australian patent.

The Court: What page is that on?

Mr. Armore: That is at the top of column 5 of the Australian patent.

By Mr. Armore:

Q. Do you have that, Dr. Prins? A. Yes, sir.

Q. Does that correspond to the second method of the application in suit? A. Yes, sir.

Mr. Armore: That is all, your Honor.

The Court: Have you any re-direct?

Mr. Ponack: Just one or two questions, your Honor.

Re-direct Examination by Mr. Ponack:

(63) Q. Is it not true, Dr. Prins, that in each case in our process we start with the monosubstituted monochloro iminodibenzyl? A. That is right.

Q. Is there any disclosure in any reference here of how to make this starting material? A. No, sir.

Testimony of Dr. Daniel A. Prins—Re-cross.
Testimony of Dr. Daniel A. Prins—Re-direct.

Mr. Ponack: That is all, your Honor.

The Court: Have you any re-cross?

Mr. Armore: Yes, your Honor.

Re-cross Examination by Mr. Armore:

Q. As for the starting materials which are used as for the substituted iminodibenzyl starting material used either in the present application, the Schindler et al. patent or the Australian patent, is there anything in the application or the patent to indicate that these starting materials are novel materials? A. They are taken for granted, and in the application I think the starting material is spelled out as being novel.

Q. Can you point out where in the application the starting material is indicated as novel? A. I will check it.

No, you are right, there is no express statement of (64) that.

Mr. Armore: That is all, your Honor.

The Court: Are you through with the witness, gentlemen?

Mr. Ponack: No, your Honor.

Further Re-direct Examination by Mr. Ponack:

Q. As a matter of fact, the application in suit here does spell out in detail how to make the novel derivative, the monochloro starting material. And, in your opinion, if this were not novel, would it be necessary to set forth the entire method of making? In your opinion, isn't the fact that the method is set forth implicitly indicative of the novelty of such starting material? A. It certainly gives the art the possibility of making the compound, which the other patents don't.

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Testimony of Dr. Murray Weiner—Direct.

TESTIMONY OF DR. MURRAY WEINER

Direct Examination by Mr. Ponack:

Q. Dr. Weiner, will you state your full name for the record? A. Murray Weiner, W-e-i-n-e-r.

Q. And your address, sir? A. 3 Thomas Way, White Plains, New York.

Q. And your education, will you elaborate on that, please? A. I have a Bachelor of Science Degree from City College of New York, and a Master of Science in biochemistry from the New York University Graduate School; and an M. D. from (66) the N.Y.U. College of Medicine.

Q. Are you a member of any professional or scientific societies? A. Yes.

I am a member of the American Board of Internal Medicine holding certification in that specialty. I am a Fellow of the American College of Physicians, a member of the Society of Experimental Biology in Medicine, the American Physiological Society, Society for Clinical Investigations, the New York Academy of Science, and the Honorary Scientific Society, Sigma XI.

Q. Have you authored or co-authored any publications? A. Yes, I have authored or co-authored about 90 publications and one book.

The Court: Medical, are they, Doctor?

The Witness: Yes, sir, all medical.

The Court: I think the Doctor is well qualified. He is a medical witness, I take it.

Mr. Ponack: In a way, yes, your Honor.

The Court: All right, he is well qualified.

By Mr. Ponack:

Q. Dr. Weiner, are you familiar with the Australian patent we are talking about in this suit? A. Yes, I am.

Testimony of Dr. Murray Weiner—Direct.

(67) Q. In connection with your present work, do you ever have occasion to engage in or have done under your supervision clinical investigations of this type of compound? A. Yes, sir. I am the Director of Clinical Pharmacology in the Carnegie Research Laboratories in connection with these compounds.

Q. In connection with this work, have you ever had occasion to test a compound which comes under the generic formula of the Australian patent? A. Yes, I have.

Q. Could you write the formula on the blackboard? A. I think I could do that.

(The witness went to the blackboard.)

Q. Write it rather large so his Honor can see it, Dr. Weiner.

The Court: Bear down heavy on the crayon. It is difficult to see up here.

By Mr. Ponack:

Q. Would you say that it would be correct to designate this compound as a 3,7-Dichloro-5-methyl-piperazinyl-propyl iminodibenzyl? A. Yes.

Q. Will you explain, if you can, how this compound comes within the scope and ambit of the generic disclosure of the Australian patent, that is what does Y and Y₁ represent there? A. Well, both Y and Y₁ are chlorides at the 2 and 7 position and A is a propyl, and R is a methyl. Then we have the compound we are now dealing with.

Q. I think you said 2 and 7 position, Doctor? A. 3 and 7 position.

Q. 3 and 7? A. Yes.

Q. Have you had occasion to test this compound or have it tested clinically? A. No, we intended to but the toxicity

Testimony of Dr. Murray Weiner—Direct.

studies in animals showed that it was far too toxic to dare give to human beings and we were forced to drop it.

Q. Are you familiar with the utility indications in the right-hand side of page 1 of the Australian patent? A. Yes.

Q. Are you also familiar with what happens when, for example, a change is made in a portion of the nucleus of a compound of this character, what can happen? A. Well, in our experience, rather radical things can happen from relatively minor looking chemical changes.

Q. Can you, for example, for the Court's edification, give us one example? A. (69) A. Well, for example, we studied the compound without the four substitutions and the simple methly-imino-propyl chain in which the propyl was an isopropyl. In other words, the nitrogen was on the second carbon rather than the third carbon; and that compound was a tranquilizer.

We then studied the compound in which the chain was a propyl rather than an isopropyl; and it was an antidepressant with no tranquilizing activity at all. It was clinically completely different. And this is not unusual.

Q. Could you correlate between the various alternatives set forth in the formula and the definitions thereunder and the various utilities set forth in the patent? A. I don't think I could make any predictions about which of these pharmacologic properties would come from which substitutions and from this generalized type.

Q. Do you see any suggestion there of utility of any of the compounds as an antidepressant? A. I see none, with the possible exception of the term "spasmolytics" which has many different conceivable interpretations; and if we choose one interpretation we might say that this might conceivably correlate with antidepression.

Q. But there is no express reference to antidepression? A. No. In fact, most of the other tests would point (70)

Testimony of Dr. Murray Weiner—Cross.

in the direction of a tranquilizer rather than an antidepressant.

Mr. Ponack: Your witness, Mr. Armore.

The Court: Cross-examine.

Cross Examination by Mr. Armore:

Q. Dr. Weiner, do you have the Australian patent in front of you? A. Yes, I do.

Q. I refer you to the recitation with respect to uses in column 2 of the patent. Do you note there that the recitation of uses includes antiemetics? A. Yes, sir.

Q. Is it generally customary to use a sedative as an antiemetic? A. Some sedatives have antiemetic properties.

Q. Would it be true that a classic sedative that is also an antiemetic as well is phenobarbital? A. I don't think I would say phenobarbital is an outstanding antiemetic. It has in some instances some antiemetic properties; yes.

Q. I have a copy of Current Therapy, 1959, and I have had photocopied certain pages from this textbook and—

The Court: What is that, a type of dictionary?

Mr. Armore: It is a medical publication which is frequently used by medical doctors, your Honor.

The Court: Are you familiar with that?

The Witness: Yes, sir, I am familiar with it.

The Court: Is it authoritative?

The Witness: It is like most books, it is not one hundred percent.

The Court: All right.

Mr. Armore: I would like to have this marked as defendant's exhibit 3 for identification.

The Court: Mark it.

The Deputy Clerk: Defendant's Exhibit Number 3 is marked for identification.

(Defendant's Exhibit No. 3 was marked for identification.)

Testimony of Dr. Murray Weiner—Cross.

Mr. Armore: And at this point I offer in evidence the Chart which was marked defendant's exhibit 2 for identification.

The Court: That is this one here (indicating)?

Mr. Armore: That is a photocopy of the chart.

The Court: It may be received in evidence.

The Deputy Clerk: Defendant's Exhibit Number 2 is marked in evidence.

(Defendant's Exhibit No. 2 was received in evidence.)

(72) By Mr. Armore:

Q. I refer you to page 591 of defendant's exhibit 3 for identification, and I would also have you compare the photocopy of page 591 with that page in the actual volume. Is that a true copy of page 591 of the actual volume? A. Yes, it is.

Q. I direct your attention to the fact that at the bottom of column 1 there is a reference to "Antiemetic Agents". Do you see that? A. Yes, sir.

Q. And on the right side near the bottom of the second column there is a reference "The Severe Case". And among "Parenteral Sedatives" is included phenobarbital. Do you see that? A. I would like to know a little more. A severe case of what? What are we dealing with here? I am not clear yet.

Q. The reference is to severe cases. A. The heading on the top of the page is "Pernicious Vomiting of Pregnancy". That is a rather specific symptom.

Q. Yes. But do you recognize that the preceding paragraph is "The Severe Case" and preceding that there is a discussion of "Antiemetic Agents"? A. Yes.

Q. Therefore, would you say that phenobarbital is a (73) common remedy for antiemetics? A. No, sir.

Testimony of Dr. Murray Weiner—Cross.

The Court: The doctor has already answered that. He said, in some cases it may be. He stated that several questions ago.

The Witness: Certainly, if you put a patient to sleep with a large dose of phenobarbital he is likely to stop vomiting, but I don't think that, therefore, deserves the classification of it as a potent anti-emetic.

By Mr. Armore:

Q. Dr. Weiner, I refer you again to the Australian patent and to the recitation as to uses. Do you see there that one pharmacological property is "antihistaminics"? A. Yes, sir.

Q. Is that synonymous with antiallergic, substantially? A. It is not synonymous. Antihistaminic is a specific case of antiallergic, it is antiallergic in those cases where the allergy is due to histamine.

Q. Is it true that in many cases the allergy is due to histamine? A. Histamine is a factor, yes.

Q. I refer you to the reference in the patent to "spasmodics". A. Yes, sir.

(74) Q. Are sedatives frequently used as an antispasmodic agent? A. Yes, sir.

Q. I refer you to the recitation of uses to "potentiators of anaesthetics and analgesics". A. Yes.

Q. Is it well known, and has it been well known for a long time prior to 1959, that sedatives are excellent potentiators for anaesthetics and analgesics? A. And a great number of non-sedative compounds also are excellent potentiators.

Q. But is it true that sedatives are also well known excellent potentiators? A. Yes.

The Court: That is the capsule they give you before you go into the operating room, is it?

Testimony of Dr. Murray Weiner—Cross.

The Witness: Yes, sir.

The Court: I thought so.

By Mr. Armore:

Q. Dr. Weiner, you have testified that you have tested this species of the compound disclosed in the Australian patent (indicating). Did you test any compound in which the methyl group was omitted from the piperazino tail portion of the molecule? (75) A. I can't—

Q. That is an unsubstituted piperazino compound? A. I can't recall all the compounds that have been tested. Many have been tested in very early pharmacologic evaluation. Relatively few reached the stage of chronic toxicity which this compound reached. So, from memory, I cannot say yes or no.

Q. Do you have any data at all to show the type of tests you made, the nature of the tests and the type of materials you worked with? Do you have any data with you whatsoever? A. In the pharmacologic—

Q. With respect to these tests that you are talking about.

The Court: Do you have any written records with you?

The Witness: The only thing I have with me at the moment is my summarizing chart of some compounds in which I have my handwritten notes which say, that in November, 1962, this compound was tested in the Woodard Research Laboratory under our arrangement and was found to be unsuited for human trial because of the chronic toxicity.

By Mr. Armore:

Q. And that is the sole note you have there? (76) A. With me. I have a complete file, of course, and a com-

Testimony of Dr. Martin Rubin—Direct.

plete multi-page document of the actual tests done back in my office.

Mr. Armore: That is all, Your Honor.

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TESTIMONY OF DR. MARTIN RUBIN

Direct Examination by Mr. Ponack:

Q. Dr. Rubin, what is your full name, sir? A. Martin Rubin, R-u-b-i-n.

Q. Where do you live? A. At 3218 Pauline Drive, Cheve Chase, Maryland.

Q. Will you summarize your education, please? A. I studied at the University of Iowa and at the City College of New York for undergraduate work with major in chemistry, and continued at Columbia University ending with (77) a Ph.D. there in organic chemistry.

Q. And what is your present position and your present work? A. I am presently Associate Professor of Biochemistry at the Georgetown University Medical School here in Washington, and I am Director of the Georgetown University Hospital Laboratory.

Q. Do you belong to any scientific or professional societies? A. Yes.

I belong to the American Chemical Society and many other societies, including the American Medical Association and the American Rheumatology Association and others.

Q. Have you had occasion to do laboratory literature studies in the field of medicinal chemistry, with particular reference to the iminodibenzyl type of compound? A. Yes. Most of my professional life, post-doctorate, has been in the field of organic, biologic and medicinal chemistry, meaning the chemistry of drugs. And more specifically,

Testimony of Dr. Martin Rubin—Direct.

two years ago I had occasion to serve as an expert in the field of iminodibenzyl chemistry in connection with an interference proceeding. And at that time I did laboratory studies in this field and also studied the literature in this field.

(78) The Court: I think Dr. Rubin is well qualified.

By Mr. Ponack:

Q. Dr. Rubin, are you familiar with Chart 2 which is on the board here (indicating)? A. Yes, I am.

Q. If you were attempting this synthesis—

The Court: Why don't you identify that? What is it, the Australian patent?

Mr. Ponack: No, your Honor, this is the attempted synthesis of the 3-chloro-iminodibenzyl. This is our own compound by a different process.

The Court: I see. Go ahead.

By Mr. Ponack:

Q. If you were attempting to carry out this synthesis and obtained a mixture of reaction products, what means would you use for identifying what you obtained? A. The most powerful tool available today for the resolution of mixtures and identification of products from reactions is the procedure of chromatography. This is a procedure which has been mentioned here as a method used to attempt to find what the Examiner claimed would have been an obvious procedure. This failed to show the formation of this compound in this particular reaction.

Q. To your knowledge, was the 3-chloro-iminodibenzyl, (79) the thing that we are attempting to synthesize here,

Testimony of Dr. Martin Rubin—Direct.

a new compound at the time of the application involved in this suit? A. Yes. I studied this literature and this compound had not been described in the scientific literature prior to this application.

Q. Is the preparation of this compound described in the application? A. Yes, this particular method of making this particular compound was described in this application for the first time.

Q. Can you point out where in the application it is described? A. If one turns in this application to page number 3 and examines the lines beginning at 22 and continuing through page 4, the subsequent page, through line number 13, the method of making this compound for the first time is described.

I might point out that this is the method which the previous witness has gone through in some many, many steps on his charts. That is actually spelled out in the application.

Q. What would you say with respect to the novelty of this method of preparation? A. It is totally novel and not previously described nor (80) contemplated.

Q. Have you had occasion to study the Australian patent 215,335 which is here involved? A. Yes, I have.

Q. What is your opinion with regard to the general formulae where you have Y and Y₁ set forth in this patent? A. This Australian patent provides a formula which is extremely broad in its connotation and encompasses within it, I would say, literally millions of possible specific compounds.

Q. Do you see any spelling out there, specifically, of the Claim 8 Compound? A. There is none.

Q. Do you see any spelling out there of a method of preparing the Claim 8 Compound? A. There is none. On the contrary, the only procedure prescribed provides for the unsubstituted symmetrical parent compound.

Testimony of Dr. Martin Rubin—Direct.

Q. I turn your attention to the description of the biological activities set forth in lines 13 to 18 of column 2 of that patent. Would you comment as to your understanding of this portion of the Australian patent disclosure? A. Well, I addressed myself very intensively to the question of whether or not it would be obvious to one starting (81) from the Australian patent to proceed to go in the direction which would lead to the specific compound of Claim 8 in this application.

And in order to do that I tried to put myself back into the time of an inventor faced with this question. And I examined the most pertinent art that I could find which would teach him which way to go. While this analogy is not a very good one, I suppose the Australian patent is synonymous with saying that there is a good American some place among the two-hundred million, go find him. I don't know why he is good even or what his name is or where he lives or anything else; but go find him.

The Court: Well, I guess another good simile would be "a flyspeck in a pot of pepper", wouldn't it?

The Witness: Yes, indeed.

And the question would be then for some inventor at this time seeking to go and make an invention in this field as to what he would turn to as a guide for seeking such a good material. So I studied the medicinal chemistry art as of this time to come up with what might have been the best analogy that I could find for an inventor at this time.

And the one I came up with, your Honor, is a classic one, and I consider this very close and the closest I could get to this particular subject. I would try to make it clear (82) as to why the inventor might have used this particular analogy.

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The subject, actually, is very similar to this one. If we turn the pages a little bit I think the Court will see the relationship in the structures. As we go a little further, yes, here is a compound which is closest in background to the one under consideration (indicating).

And your Honor will see that as in our second example we have the two ring systems on both sides, we have the nitrogen in the middle, and we have a bridging compound with a bridging group, the CH group, at the top rather than in our present one, the CH₂—CH₂, which was new at the time of this application.

But in addition, as is clear here, this particular structure has again, as the Australian does, the two possible substituents, Y and Y'.

And the question is, if an inventor facing the Australian patent were to go and look for improving that patent and went to this very close art, where would it lead him? And it leads him, if your Honor follows this start, it leads him, as is now here well described classically in the book by Adrien Albert entitled "Selective Toxicity"—and I have the book here and we have prepared copies of several pages—

(83) Mr. Ponack: May we have these pages marked for identification, your Honor?

The Court: What is it?

The Witness: This is the title page and pages 154, 155, 200, 201, 202, 203, 204 and 205.

The Court: It may be marked.

The Deputy Clerk: Plaintiff's Exhibit Number 5 is marked for identification.

(Plaintiff's Exhibit No. 5 was marked for identification.)

The Court: Have you a copy for Mr. Armore?

Mr. Ponack: I had prepared them this morning, your Honor—

Testimony of Dr. Martin Rubin—Direct.

The Court: Well, it is just about time for the noon recess. You will probably be able to find them during the recess.

Mr. Ponack: Yes, your Honor.

The Deputy Marshal: This Honorable Court stands recessed until 1:45 this afternoon.

(Whereupon, at 12:28 a. m. the Court recessed as noted.)

(84) (Afternoon Session, 1:45 p. m.)

The Court: Dr. Rubin may resume the stand.

By Mr. Ponack:

Q. Dr. Rubin, would you briefly sum up what you were testifying to before the recess? And you may continue.
A. Getting right to the point, the question I addressed myself to was, starting with the Australian patent, which I have written for the purposes of this immediate summary on the board, would it have been obvious to someone at that time with the normal skill in the art to have been led directly then to the compound of Claim 8 in this case? I answered, no, and I said that the closest thing I could find in a survey of this art was the compound listed as the reference compound on the bottom of the blackboard, and that if one had studied the history of this compound, again, where there are innumerable possibilities of which 100 had actually been tested, one was found to be useful. The compound that was found to be useful was a symmetrical substitution, not an unsymmetrical one, as the Patent Office would suggest the Australian teaches. And, further, the compound of utility was not a chloro compound. So on both counts, as near as I could evaluate the situation, someone starting at that time with the Australian patent would be led (85) away from the particular compound of Claim 8 rather than to it. So I concluded that it was not an obvious compound.

Testimony of Dr. Martin Rubin—Direct.

Q. For the record, will you name that compound at the lower half of the blackboard? A. Yes, the compound at the lower half is called Acridine, and these are substituted acridines and they are fully described in the material contained in the Appendix of plaintiffs' exhibit 5.

Q. Do you mean in the Adrien Albert book? A. Yes, in the Adrien Albert book which has been brought in for the purposes of identification.

The Court: You now have a copy of that, Mr. Armore, have you not?

Mr. Ponack: I gave Mr. Armore the book itself, your Honor.

Mr. Armore: Is that what you are referring to (indicating)?

Mr. Ponack: Yes.

We haven't offered it in evidence yet.

Mr. Armore: Your Honor, should I make an objection now or wait until it is offered?

The Court: Wait until it is offered.

By Mr. Ponack:

Q. Dr. Rubin, I direct your attention to the Schindler et al. patent 2,813,857 and ask whether you are familiar (86) with that patent? A. I am.

Q. Will you summarize what it discloses to you? A. Again, the question is, would it have been obvious starting with the Schindler patent to be directed, once more, to plaintiffs' here designated Claim 8 compound? This is really the question at issue.

The Court: That is right.

The Witness: And I, again, for the purposes of summary, on the other side of the board indicated my reasons why I feel this is absolutely not so.

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This is work that was done in my own laboratory by myself and, incidentally, a reference to it is in the same book, and I have cited that page in the book.

Let me point out the significance, if the Court will permit. The top compound (indicating to the blackboard) is the Schindler et al. patented compound, which is a symmetrical, again, dichloro substituted compound.

The work we did is listed on the bottom in three parts. Under column 1 is a vitamin. It is called para-aminobenzylic acid. It is a very important element in nutrition.

If you take this material and proceed to make a symmetric dichloro substitution you convert the vitamin activity to an extremely weak vitamin activity. And, as we (87) have shown, if you take then the next step and make the asymmetric monochlor substituent, such as the compound under Claim 8 under discussion here in type, you not only convert from a weak vitamin but totally to an anti-vitamin. It is a completely contrary activity.

And, therefore, at the time of this art, if one had started with Schindler's patent and said, well, all right, we have a symmetric dichloro, let's make it an asymmetric dichloro, he would have expected to find it a totally contrary activity.

I concluded, therefore, that the conversion on these grounds of chemical thinking and biologic thinking would have been unobvious and, therefore, actually indicate a high order of inventivity, particularly in light of the fact the compound, the monochloro, had not been disclosed, it was new, and it took a lot of persistence to make it and test it. This is the basis of my conclusion.

Q. Would you then summarize with respect to the art of record here, that is the Schindler et al. and Australian

Testimony of Dr. Martin Rubin—Direct.

patents, and considering the Schindler et al. patent alone, or the Schindler et al. patent in the light of the Australian patent? In other words, would one of these patents alone or the combination thereof lead one of ordinary skill in the art at the time this invention was (88) made to the present compound of Claim 8? A. On the basis of the studies and the description I have made, I would conclude that neither the Schindler et al. patent nor the Australian patent, nor the combination of the two of them would have led someone at that time facing this field to the preparation of this new Claim 8 asymmetric chloro compound.

Q. And the work which you testified to with respect to the PAB, para-amino-benzylic acid, is summarized in this book by Adrien Albert and you are given credit for it; is that right? A. That is correct.

Mr. Ponack: I offer plaintiffs' exhibit 5 for identification in evidence, your Honor.

Mr. Armore: I object, your Honor, on the ground there are many references in that book to work by others and it amounts to hearsay. It is not an authoritative work.

The Court: Overruled. Mark it in evidence.

The Deputy Clerk: Plaintiffs' Exhibit Number 5 is marked in evidence.

(Plaintiff's Exhibit No. 5 was received in evidence.)

Mr. Ponack: That completes the direct examination, (89) your Honor.

The Court: Cross-examine.

Mr. Armore: May it please the Court, at this time I offer in evidence defendant's exhibit 3 which was previously marked for identification.

The Court: Have you any objection to the receipt of this into evidence?

Mr. Ponack: I don't recall what it is.

Testimony of Dr. Martin Rubin—Cross.

The Court: You had better look at it.

Mr. Ponack: I have no objection, your Honor.

The Court: Without objection it may be received.
Mark it.

The Deputy Clerk: Defendant's Exhibit Number 3 is marked in evidence.

(Defendant's Exhibit No. 3 was received in evidence.)

Cross Examination by Mr. Armore:

Q. Dr. Rubin, in your earlier remarks you indicated that there were procedures disclosed in the present application in suit with reference to the method of preparing the iminodibenzyl intermediate; and I assume you referred to the paragraph bridging pages 3 and 4. I didn't quite get the numbers of the pages you mentioned. (90) A. I did.

Q. Those were the only pages in the specification of the application you had reference to; is that correct? A. That is correct.

Q. Now that paragraph indicates very generally the general procedures that can be followed in forming the unsubstituted and forming the substituted iminodibenzyl intermediate; is that correct? A. No. The paragraph stipulates specific reactions that may be used to do this.

Q. Is there any example in that application giving a specific exemplification of the procedures specifically used in specific terms for the preparation of the monochloro-iminodibenzyl? A. No, there is not.

Q. In view of the fact that there is no specific disclosure by way of a specific example—I withdraw that question. Dr. Rubin, you based your testimony with respect to the unobviousness of the monochloro compound from the dichloro compound of Schindler et al. on the basis of an

Testimony of Dr. Martin Rubin—Cross.

analogy with this one compound which is a carboxyaniline and substituted with a chlorine, two chlorines or substituted with one chlorine; is that correct? A. That is correct.

(91) Q. That is the sole basis or the sole analogy upon which you predicate your opinion that the monochloro would not be obvious from the dichloro; is that correct? A. It was the best analogy that I could find in a survey of the entire literature.

I think it is necessary to point out that at the time of this invention the field under discussion was a new one. There were no other guides available.

Q. Isn't it true, Dr. Rubin, that in the field of pharmacology or chemistry and biochemistry, that one normally expects compounds which have similar molecular structure to have similar biochemical or physiological or other properties? A. No.

No, because the sum total of the effective material in the organism is an exceedingly complex one, and we have now gone into the entire era of recognizing that very minute changes in structure can make profound differences in function; and this is the reason why I answered no.

Q. Therefore, would it be correct to say, that there are a number of instances in which small changes in structure will accomplish substantial changes in function? A. Yes.

The Court: Wasn't that true of aspirin?

(92) The Witness: Was it true of aspirin, your Honor?

The Court: Yes.

The Witness: Yes, there are many types of aspirin.

The Court: I mean Bayer's Aspirin.

The Witness: Thousands have been tested and we still have one which is functional.

Testimony of Dr. Martin Rubin—Re-direct.

By Mr. Armore:

Q. Isn't it also true that in many cases, however, small changes in structure, such as a change in a substituent, will not materially affect the properties of a substance? A. I would agree.

Q. And that notable examples of those would be basic compounds, such as penicillin and the salts of penicillin? A. There I would have to disagree because if you examine the chemistry, not salts, salt is a different class—you said penicillin and salts, and I think we ought to try to be clear. If you examine the chemistry of penicillin, very minor differences make for total inactivity in the penicillin; and minor differences also make for marked improvement. So this is a difficult field if one starts with a general formula that can give a million—this is a bad number but I use it—or a lot of examples. It takes a considerable amount of hard ingenuity to arrive at one which will be useful in a human.

(93) Q. Apparently, I selected a bad example. But the fact does remain, Dr. Rubin, as you have indicated, that there are many compounds where small changes in the structure will still result in the compounds having generally similar properties? A. I don't like many, but I am certainly willing to accept some. There are some.

Mr. Armore: That is all, your Honor.

The Court: Have you any re-direct?

Mr. Ponack: Just one question, your Honor.

Re-direct Examination by Mr. Ponack:

Q. With respect to the disclosure of how to make this compound, would the art still have any difficulty following that disclosure with reference to the Friedel-Crafts and Schmidt processes, etc., in making our compound? A. No, this is standard organic chemistry.

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Testimony of Dr. Ernest B. Sigg—Direct.

(94) TESTIMONY OF DR. ERNEST B. SIGG

Direct Examination by Mr. Ponack:

Q. Dr. Sigg, what is your full name, please? A. My full name is Ernest B. Sigg, S-i-g-g.

Q. And where do you live? A. My address is 796 Long Hill Road, Briarcliff, New York.

Q. Will you give us your education, please? A. I was educated in Basle, Switzerland where I received a Master's Degree in Chemistry in 1947 and my M. D. Degree in 1949.

Q. And what memberships, if any, do you have in scientific and professional societies? A. I am a member of the American Physiological Society, of the American Pharmacological Society and I am a Charter Member of the American College of Neuropsychopharmacology. And I am a member of the New York Academy of Sciences and of the Swiss Medical Association.

Q. What is the nature of your present work? (95) A. Presently I am employed by the Geigy Research Laboratories. I have the position there of Director of Pharmacology. My main interest is particularly the effect of drugs on the central nervous system.

Mr. Ponack: If your Honor please, do we need more?

The Court: No, he is well qualified.

By Mr. Ponack:

Q. Are you familiar with the mono and dichloro compounds here involved? A. Yes, sir, I am.

Q. Have you had occasion to do any testing of these compounds? A. Yes, I have.

Q. In what respects did you test these compounds? A. We tested these compounds in regard to their effect on the central nervous system.

Testimony of Dr. Ernest B. Sigg—Direct.

Q. Will you explain to his Honor just what you did and what results you obtained? But before you do that would you please look at these charts to see if you are familiar with them so we can have them identified? A. Yes, I am familiar with them.

Q. And you have a set of these? A. I have a set, yes.

(96) Q. Who did the work that is represented on these charts? A. The work which is represented on these charts was done under my supervision by Dr. Gyermek.

Mr. Ponack: Would you mark these for identification?

The Court: Do you want them in as one exhibit?

Mr. Ponack: Yes, your Honor.

The Deputy Clerk: Plaintiffs' Exhibits 6 and 6-A are marked for identification.

(Plaintiffs' Exhibits Nos. 6 and 6-A were marked for identification.)

Mr. Ponack: Would your Honor like a set of these, because we are going to talk about them?

The Court: Yes.

By Mr. Ponack:

Q. Would you explain to his Honor what you did, why you did it, what happened, what the significance of these charts are and what the results were, particularly with respect to the compounds as to whether they are similar, dissimilar or involved a difference in kind or a difference in degree? This is a long question, but I think it will be easier if you yourself take care of it without me interrupting you. (97) A. Your Honor, these two charts represent an experiment which is commonly done in a modern laboratory to evaluate CNS activity of a compound.

Testimony of Dr. Ernest B. Sigg—Direct.

It involves creating in an experimental animal—and in this case we are using mice—depression. Naturally, depression does not occur, as far as we know, in animals, but with reserpine you can induce one. Reserpine is an alkaloid which is used in man to lower blood pressure and it is also used as a tranquilizer.

The Court: As a tranquilizer it depresses?

The Witness: It depresses pain.

The Court: Does it diminish the heartbeat?

The Witness: It diminishes the heartbeat too, yes.

The Court: Go ahead.

The Witness: The mice treated with reserpine showed no locomotor activity. They don't run around, they just sit there and don't move around.

We have a runway for these mice and by giving them a standard stimulus we measured the length of the run. They would run a certain length down the runway.

Now you have two charts, I think, in front of you. One is Number 3 where you see the number G-28.364. This is a code number which we gave to this oral agent, and in this case it represents the dichloro dimethyl-amino-propyl-iminodibenzyl.

(98) By Mr. Ponack:

Q. That is the compound of the Schindler et al. patent?

A. Yes.

Now on this curve you see that the coordinate is calibrated in inches. That indicates how far these mice run.

On the abscissa you find several points. C represents the control. That is as far as a mouse runs under controlled conditions having received reserpine.

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Then you find, 3, 10, 30 and 60 minutes, which represents the time of the tests after they have been injected with the test compound, that is the dichloro compound. You see that repeated three times, which indicates that it has been done with three different doses which we inject into the animal. And you see the curves, these various points, they are practically flat. In other words, there is no change from the control after the injection of the dichloro dimethylamino-propyl-iminodibenzyl compound.

Now, if your Honor please, we will go to the chart number 4. There you see the code number G-34.586, which stands for the monochloro-dimethylamino-propyl-iminodibenzyl.

Q. Which is the compound of our claim 8? A. Yes, that is the compound of our claim 8.

Again, you see the alternates representing the lengths of the run and the abscissa, the controls C, and what a mouse does 3, 10, 30 and 60 minutes after injection. (99) Again, at the three different dose levels which you will find across on the top of the chart 1, 3 and 9 milligrams.

And as you can see, your Honor, after injection of the mice with the monochloro compound they run more than the controls. In other words, you see a definite curve moving along the alternate of this graph.

The conclusion of these results is that this compound is an active compound in this so-called reserpine antagonist test.

Q. Then, Dr. Sigg, your opinion with respect to this is that it indicates that the compounds are significantly different, insignificantly different, or what? I mean with respect to these two compounds, what does this mean? A. These two compounds are significantly different from each other.

Q. Have you had occasion, Dr. Sigg, to become acquainted with certain affidavits which are of record in this case which

Testimony of Dr. Ernest B. Sigg—Direct.

I will refer to as the Wirz affidavits? These affidavits are papers number 6-A and 6-B in plaintiffs' exhibit 1.

The Court: Were they before the Patent Office?

Mr. Ponack: Yes, sir, they are in the record in this case.

The Court: All right.

By Mr. Ponack:

(100) Q. And the Kunz affidavit, which is paper number 17 in plaintiffs' exhibit 1. These were all before the Patent Office. Would you look at these again, if you need to and— Oh, you have copies right there? A. I have copies.

Q. Do you recall what tests were carried out by Dr. Wirz? A. Yes.

Q. Explain, very briefly what the tests were, what the results were, and then we will go on to the Kunz affidavit.

Mr. Armore: Objection, your Honor.

The Court: Why?

Mr. Armore: On the ground that the witness has not been sufficiently linked with the affidavits.

The Court: Have you seen those affidavits?

The Witness: Yes, I have.

The Court: Have you studied them?

The Witness: Yes, I have.

The Court: And you know what they are all about?

The Witness: Yes, I do.

The Court: The objection is overruled. Go ahead.

By Mr. Ponack:

Q. Where were we? A. You asked me to describe the tests contained in the (101) affidavits of Wirz.

Testimony of Dr. Ernest B. Sigg—Direct.

Q. Yes. Tell us what tests were carried out, whether they are standard tests and, very briefly, what the results are with particular reference to the two compounds here involved.

Mr. Armore: Your Honor, may I respectfully interpose one more objection on the ground there is no indication that the witness was present when the tests were performed.

The Court: He doesn't have to be. Overruled. Go ahead.

By Mr. Ponack:

Q. Go ahead, please, Dr. Sigg. A. There are two tests described which are currently used in pharmacology laboratories. One, in principle, concerns a technique in isolated tissues where the contraction of an isolated cut is measured and its relaxation is studied after addition of test compounds. One finds with this test compounds of atropine-line activity.

The Court: That is the same thing they use in dilating the pupil of the eye, atropine?

The Witness: That is correct.

The Court: Go ahead.

The Witness: The second test described is a test in which a hormonal substance is used to induce the swelling of the paw injected. And, again, test drugs are injected to (102) find out how antagonistic they are against this such induced swelling.

Q. Now evaluating the results which were obtained in the light of what Dr. Kunz says in his affidavit— Well, would you first tell us what Dr. Kunz says in his affidavit and whether or not you agree? And in the light of that,

Testimony of Dr. Ernest B. Sigg—Direct.

will you evaluate the monochloro and dichloro compounds used in these two tests, the gut test and the rat's paw, with respect as to whether they are significantly different or not? A. Sir, do you want me to read the conclusions?

Q. No, you just summarize them yourself in your own words, your understanding of them.

The Court: Are those in evidence?

Mr. Ponack: They are all in evidence.

The Court: Well, why not ask him whether or not he agrees? Then he won't have to repeat what is in them.

By Mr. Ponack:

Q. Do you agree with what is said in Dr. Kunz's affidavit? A. We have been talking about Dr. Wirz's affidavit.

Q. No, let's go now to Dr. Kunz's affidavit, which is an evaluation of Dr. Wirz's affidavit. A. Yes.

Q. Do you agree with the standards which he sets up (103) for evaluating the results in the Wirz affidavit? A. Yes, your Honor, I fully agree.

Q. Will you summarize what this means? Does this mean that the compounds are significantly different, or one is practically useful and the other is not, or vice versa, or what? A. It means that the two compounds in question are different in kind.

Q. The Patent Office has said that these affidavits show a difference in degree. Do you agree with that? A. No, I do not agree.

Q. Why not? A. Because they are different in a quantitative sense in order of magnitude, so that we have to come to the conclusion that they are inactive.

Q. Which are inactive? A. Well there are—I have to refer—

Q. Direct your attention only to the monochloro and the dichloro. A. Oh, the dichloro is inactive.

Testimony of Dr. Ernest B. Sigg—Cross.

Q. And the monochloro? A. The monochloro is very active.

The Court: Then they are antithetical, are they not?

(104) The Witness: Pardon?

The Court: They are antithetical then, are they not? One is the antithesis of the other?

The Witness: Yes, sir.

The Court: Go ahead.

By Mr. Ponack:

Q. Would you say that this is a correct statement? Regardless of what the other properties of these two compounds is, the dichloro and the monochloro, in view of the results which you have obtained and which Dr. Wirz has obtained, would it be correct to say that these two compounds have different spectra of properties? A. Yes, I certainly would.

Q. Would these spectra be significantly different? A. Yes, sir, they are significantly different.

Mr. Ponack: That is all, your Honor.

The Court: Cross-examine, Mr. Armore.

Cross Examination by Mr. Armore:

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(112) Q. Dr. Sigg, you have testified with respect to two affidavits by Wirz which are in the record of the present application; is that correct? A. That is correct.

Q. Now were you present when these experiments were performed? A. No.

Q. Were you in charge of these experiments at all? A. No.

Q. Did you have any direct connection with these ex-

Testimony of Dr. Walter Joseph Pöldinger—Direct.

periments? A. I had direct connection insofar as I have seen the setups in which these tests were done repeatedly.

Q. Did you see the results which were achieved? A. I saw the results; yes.

Q. You saw all the results which is represented by the data in these affidavits? A. That I could not tell you, sir.

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(116) Q. With respect to the affidavit, the Wirz affidavit, showing the comparison between the Australian patent—the compounds of the Australian patent—and the compound of Claim 8, I refer you to page 2 and 3 of the affidavit.

Now compounds 3 and 4 represent compounds corresponding to those in the Australian patent, do you recognize that? A. That is correct.

Q. However, each of the compounds are substituted in a piperazino radical; is that correct? (117) A. That is correct.

Q. Were any tests made with compounds that were not substituted with the piperazino radical? A. I am not aware of this.

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(119) TESTIMONY OF DR. WALTER JOSEPH PÖLDINGER

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Direct Examination by Mr. Ponack:

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Q. What is your full name, Dr. Pöldinger? A. Walter Joseph Pöldinger. P-o-e-l-d-i-n-g-e-r.

The Court: When you put the "e" in you don't use the o dot (ö), do you? The oomlout?

Testimony of Dr. Walter Joseph Pöldinger—Direct.

The Witness: That is right.

By Mr. Ponack:

Q. And your address? A. Basle, Switzerland, Schuttenmattstrasse 61.

Q. Would you outline your education for us, Dr. Pöldinger? A. I have studied medicine at the University of Vienna, and I received the degree in 1953 of Doctor of Medicine.

Then I worked at the University Clinic for Psychiatry and Neurology in Vienna; and then for three years in a General Hospital in Vienna. Since 1957 I worked in the mental hospital of the State of Lucerne in Switzerland; and since 1963 I have been Chief of the Department of Clinical Psychopharmacology at the Psychiatric Clinic of the (120) University of Basle.

Q. And what professional societies do you belong to, Dr. Pöldinger? A. I am the Chief of the Department—

Q. Yes, I understand, but what professional societies do you belong to? A. I am a member of the Austrian Medical Association, a member of the Austrian Association for Electroencephalography, a member of the Austrian Anthropological Association. I am a member of the International Association for Neuropsychopharmacology; and I am Treasurer of the International Association for Suicide Prevention.

Q. And do you have any publications in your own name?

A. Yes. I have 40 papers and one book. Most of them concern problems of psychopharmacology; also the book.

Q. Have you had any work in the field of iminodibenzyls?

A. I have written 3 papers concerning clinical experiences with iminodibenzyls.

Mr. Ponack: Has the witness been sufficiently qualified, your Honor.

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The Court: Very satisfactory. He is well qualified.

By Mr. Ponack:

(121) Q. Dr Pöldinger, I call your attention to an affidavit by Walter Pöldinger. Are you the affiant? Do you recognize this affidavit? A. Yes.

Mr. Ponack: Your Honor, this is paper number 10 in plaintiffs' exhibit 1.

By Mr. Ponack:

Q. Were the tests reported in the affidavit carried out by you or under your supervision? A. All by myself.

Q. Will you state whether or not the test procedure you utilized is a standard procedure in this field? A. It is a standard procedure.

Q. Now would you look at page 4 of that affidavit, and referring to, for example, Case No. 1, would you tell us in some detail, not too much detail but reasonable detail, because we would like to finish today, what you did, why, and what the results were that were obtained? Also tell us what compounds you used, what patient you used and what were the symptoms.

The Court: Isn't that all set out in the affidavit?

Mr. Ponack: It is more or less set out. It is not set out in detail. I suggest, your Honor, that we be permitted to go through one case.

(122) The Court: Very well.

The Witness: We used the dichloro compound.

By Mr. Ponack:

Q. This is the dichloro compound? A. The dichloro compound. And we used a male patient suffering from

Testimony of Dr. Walter Joseph Pöldinger—Direct.

indogenous depression and we controlled all his symptoms when he came to the clinic. And then we gave him 3 times a day an injection of 25 milligrams of the compound.

Q. Which compound? A. It was the dichloro compound.

Q. That is the compound of the Schindler et al. patent?

A. Yes, sir. And during a period of 3 days we could not see any change in the behavior of the patient and, therefore, after the period of 3 days we gave him a higher dosage 3 times a day, 2 ampules for 25 milligrams. That means at every time 50 milligrams of the dichloro compound during a period of 2 days; and we also did not see any change with the higher dosage.

Q. You were trying to discover—if I am wrong, please correct me—whether this compound would act to eliminate the depressive mood, that is whether it would act as an antidepressant; and the results were positive or (123) negative? A. Negative.

Q. It did not eliminate the mood? A. No.

Q. Now we have on the same page in the affidavit 10 cases of this character. Briefly, so that you won't have to go through all of them, how do these compare with the case 1 to which you just testified? Was the work about the same and were the results about the same? A. The same results. We have not seen any change of the mood or of motor activity.

Q. So that the dichloro compound does or does not—
A. There was no activating effect.

Q. Do you mean there was no stimulating effect? A. Yes, no stimulating effect.

Mr. Ponack: Your Honor, I have to help this witness a bit because of the language difficulty.

The Court: I understand.

By Mr. Ponack:

Q. Now let's go through case No. 21 on page 5 of the

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affidavit. A. Case 21 refers to a patient suffering depression because of depressed schizophrenia. And in this case we, during a period of six days, 3 times a day, administered 25 (124) milligrams of the dichloro compound perorally and we observed no change during the period on drive and mood.

Q. How about this general condition? A. No effect, no stimulating effect, and the general condition was growing worse.

Q. How about all the other tests on the depressed schizophrenics with the dichloro compound, what were the results, in general, as set forth in this affidavit? A. We observed no activating or stimulating effects.

Q. What else did you do in this investigation as reported here in your affidavit? What other work did you accomplish? A. The next compound?

Q. Yes. A. The monochloro compound—

Q. You didn't do any more with the dichloro? A. No.

Q. Why not? A. Because there was no effect, and from the ethical point of view—

The Court: I think that is quite clear. How about the monochloro?

By Mr. Ponack:

Q. Now doctor, his Honor would like you to continue (125) with the monochloro. Now tell us what the results were with the monochloro compound. That is on page 7 of the affidavit. A. The results with the monochloro compound on endogenous depression or depressed schizophrenia were that we observed a strong stimulating effect on the mood and motor activity.

Q. And how about on page 8 of the affidavit? Just in general, I think, will be sufficient. A. In general, we have also seen a strong activating effect on drive and on mood.

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Q. Now there are various types of schizophrenics. Did you use what are called matched schizophrenics and explain this, if you did? A. Most schizophrenics suffer from hallucinations and paranoid ideas. But this type of schizophrenic suffers from depression. He has no paranoid ideas and no hallucinations but he has a depressed mood and is inactive in motor activity.

The Court: How about the catatonic type?

The Witness: It is not the same type. Catatonic is only inactivity of drive. But they were also depressed in the moods.

The Court: I see.

By Mr. Ponack:

Q. In summary, what is the significance of the tests (126) reported here from the standpoint, for example, of the identity, or the lack of identity, or the significant difference or lack of significant difference between the test compounds? A. We have found a significance because the dichloro compound has had no effect and the monochloro compound has had a very strong effect on depressive states.

The Court: Stimulating effect?

The Witness: Yes, sir.

By Mr. Ponack:

Q. Was any other work done with the dichloro compound, as far as you know? A. With the dichloro it was not possible because it was necessary to stop the investigations. With the monochloro I have later on made other investigations but I have not published them.

Q. And in all these other investigations, what were the

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results with respect to the monochloro? A. The same as I have written in this affidavit.

Q. In other words, you got the same results? A. I got the same results with more patients later on.

Q. And what are those results? A. A good stimulating effect in depressive states.

(127) Q. In paper number 1 of Plaintiffs' Exhibit number 11, the Examiner states, with respect to this affidavit, and here I quote:

"There is no showing that the monochloro compound would have been effective against the patients to which the di-chloro compound was administered and found to be ineffective."

The Examiner also states:

"It is consistent with the affidavit that the monochloro compound would also have been ineffective against these patients."

Do you agree with these statements by the Examiner? If you do, explain why, and if you don't agree, tell us why. Do you understand what the Examiner said here? A. Yes, I understand.

Patients suffering severe depressions can be administered, from the ethical standpoint, only one new drug. They are suffering severe depressions and there is always the danger they will try to commit suicide. We are not allowed to administer more than one new drug. When the new drug is found to be not acting we cannot change to another new drug on the patient. You can do this in a pharmacological experiment with animals but cannot do it in the clinic. If you administer a new drug that does not act you have to give after a short period in the (128) next treatment a drug that is well-known to

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the doctors because you are not allowed to give to a patient during a long period insufficient medication.

Q. Dr. Pöldinger, also the Examiner states in the same paper number 11, and here again I quote:

“There is no showing to indicate that the di-chloro compound would not also have been effective against the patients which were shown to respond to treatment with the mono-chloro compound.”

How do you know that the dichloro would not have worked on these patients who responded to the mono-chloro? Let's have the benefit of your viewpoint here.
A. It is the same thing.

Q. How was the selection made of the patients involved in your tests? A. There was no selection. Every patient suffering depressions coming into the clinic got the treatment. There was no special selection.

Q. In its decision, the Patent Office Board of Appeals said: “The Poldinger affidavit, paper no. 10”—that is this— “. . . is not persuasive since said affidavit indicates that the Schindler et al. compound has the same utility as the claimed compound and differs therefrom merely in degree.” Do you agree with this evaluation? (129) A. No.

Q. Will you please explain? A. The dichloro compound has had no effect and the monochloro compound has a strong effect.

Q. What would you say about the spectrum of properties of the two compounds? A. The one compound has no spectrum of properties.

Q. I mean as far as treatment of endogenous depression? A. There are two target symptoms, depressive mood and motor inactivity. One compound has a good effect and the other one has no effect.

Mr. Ponack: That is all.

The Court: Cross-examine.

Testimony of Dr. Walter Joseph Pöldinger—Cross.

Cross Examination by Mr. Armore:

* * * * *

(136) Q. Doctor, you testified on direct examination—Strike that, please. Do you recognize that in research involving psychiatric drugs that the expression is frequently used that patients are their own best control?

The Court: Patients are their own best control?

The Witness: No, that is not true in depressive patients because depressive patients like to go out sometimes and commit suicide. They say to the doctor, oh, I am very well, let me go home; I am well now. And he tries to do this so he can go out and commit suicide. And, therefore, it is not always true what a patient says when he is suffering endogenous depression.

By Mr. Armore:

Q. Did you understand my question, Doctor, as to patients being their own best control?

The Court: What is that control? What does the word mean in that particular context?

Mr. Armore: In that context it means, your Honor, that patients can be given different various drugs being (137) tested at different times at sufficient intervals in order to determine the nature of the reaction, because different patients react differently and at different stages of their conditions.

The Court: Now do you understand what that means, Doctor?

The Witness: Yes, sir.

The Court: All right, he may answer.

Testimony of Dr. Walter Joseph Pödlinger—Cross.

By Mr. Armore:

Q. Doctor, you testified that you were reluctant to give a patient who had been treated with a drug which had no effect when he was psychotically depressed a drug which might have a beneficial effect. Would you not—

The Court: Could there be side effects in that event?

The Witness: There could be side effects.

The Court: I would think so.

By Mr. Armore:

Q. If a patient had been insufficiently treated by one doctor or another doctor and subsequently he went to a second or third doctor, and in the interval a better drug had been developed for his condition, would the second doctor refrain from using the better drug because the patient had earlier been given an ineffective drug?

(138) The Court: He might wait until the effects of the first drug was out of the patient's system if he were a good doctor.

Mr. Armore: Precisely, your Honor, and that was my point.

By Mr. Armore:

Q. Now, under the circumstances, would it not have been a more valid test, after having used the dichloro compound and no results were achieved to wait for a period of time until the drug was out of the patient's system and then try the monochloro drug to see whether that drug would have an effect? A. That is not possible. You can do that in the laboratory with animals, but with man suffering

Testimony of Dr. Walter Joseph Pöldinger—Cross.

endogenous depression and with the will to commit suicide, you cannot wait for a period of one or two weeks until the first drug is out of the body and then give him the other drug. That is not possible in medicine.

Q. These patients that were tested, was there an examination made to determine the current physical condition of these patients at the time they were tested? A. Yes. Every patient who comes to the clinic is first examined for his physical condition. And we determine the physical condition by laboratory controls during the (139) tests.

Q. Was a complete medical history of each patient secured? A. There was a complete medical history taken on each patient.

Q. I assume there was a complete psychiatric history taken on each patient too? A. Yes.

Q. Were the patients who were treated with the dichloro and monochloro considered comparable insofar as their physical and medical conditions were concerned?

The Court: What do you mean, were they all in good health?

Mr. Armore: Yes, sir, were they all in good health.

The Witness: They were in good health.

By Mr. Armore:

Q. Did you personally examine these patients to detect the symptoms you recorded in your affidavit? A. I have personally seen all the patients.

Q. You made these observations yourself? A. I made them myself.

Q. Did you administer the drugs yourself? A. I administered the drugs myself. I prescribed the (140) drugs myself.

Testimony of Dr. Walter Joseph Pöldinger—Cross.

Q. You knew which patients had which drug? A. I knew it; yes.

Q. At the time you examined them? At the time you examined the patients who had the dichloro drug you knew they had been given the dichloro drug; and when they had the monochloro drug you knew they had that? A. Yes.

Q. Were the patients examined at intervals after the periods indicated in the affidavit in order to determine whether those patients given the monochloro drug had regressed or deteriorated with respect to the immediate improvement you had observed? A. I beg your pardon.

Q. I will repeat it. With respect to the patients—

The Court: How long did the effects of the drug you administered last? Would the patients have a recession afterwards?

The Witness: When we had a good effect then it was that they wanted to go home; and it was not possible to give them any longer the new drug because we are not allowed to give them a new drug when they are out of the hospital.

(141) The Court: I see.

The Witness: Therefore, it was necessary to change to one of the well-known antidepressive drugs and send them home.

By Mr. Armore:

Q. May I direct your attention to page 7 of the affidavit, Doctor? A. Page 7?

Q. Page 7, with respect to endogenous depression, duration of treatments 2 days and 9 days. A. Yes.

Q. Does that mean that the patient was treated for 9 days with the monochloro compound? A. That is 9 and 2, 11 days.

Testimony of Dr. Walter Joseph Pöldinger—Cross.

Q. That is 11 days total? A. Yes.

Q. And he was under observation for 11 days, is that correct? A. He was under observation for a longer period.

Q. How much longer? A. All the patients were under observation between one and two weeks after successful treatment with the new drug because then we had the period to change to one of the well-known drugs which we must give the patient before we send (142) him home. And then we have to look for a period of one or two weeks because there is always a possibility that he will have a change of his mood. We have to wait for this period and then we send him home and see him later after two and four weeks for a control but only for some minutes.

Q. Were each of these patients seen two, four, six and eight weeks after these tests? A. Yes.

Q. In order to determine whether the improved condition persisted? A. Yes.

Q. Each of these patients were so seen? A. Yes.

Q. With respect to the patients who were unsuccessfully treated, as indicated in the affidavit, were these patients observed for a period of time at intervals of weeks in order to see whether there was a delayed effect? A. It is always so. We always control. It is the standard method of our clinic.

Q. For example—

The Court: He answered that question, didn't he?

Mr. Armore: Yes, your Honor.

The Court: All right, don't repeat it.

By Mr. Armore:

(143) Q. I notice, Dr. Pöldinger, that with respect to endogenous depression the affidavit indicates results with respect to 10 persons or patients who were given the

Testimony of Dr. Walter Joseph Pöldinger—Cross.

dichloro compound, and it indicates that 4 patients were given the monochloro compound. Were any more than 4 patients given the monochloro compound?

The Court: What difference does that make?

Mr. Ponack: He has already answered it, your Honor, in the record.

The Court: I know it.

Mr. Armore: Your Honor, the difference is simply if there had been adverse results there is a disproportionate comparison between the number of patients who were treated—

The Court: Wouldn't that depend on the particular idiosyncracies of the person's makeup?

Mr. Armore: Your Honor, I believe I have another point in mind.

The Court: Go ahead.

Mr. Armore: More persons were treated with the dichloro compound than with the monochloro compound.

The Court: Suppose they were. What then? Would that have anything at all to do with the effects of either of the drugs?

Mr. Armore: The inference is that more patients (144) than are reported in the affidavit were treated with the monochloro compound and may have had adverse results which were not reported.

Mr. Ponack: Many more cases are in the record with respect to the monochloro, and he testified that more monochloro investigations were done by him.

The Court: Don't pursue this any further.

Mr. Armore: Yes, sir, your Honor.

By Mr. Armore:

Q. Was the Schindler et al. patent, which is the dichloro compound, assigned to Geigy Chemical Corporation, your employer? A. Yes, it was assigned to Geigy.

Testimony of Dr. Felix von Mendelssohn—Direct.

Mr. Ponack: Are you employed by Geigy?

The Witness: No, sir.

Mr. Armore: I am sorry. I thought you were.

By Mr. Armore:

Q. To your knowledge, was the dichloro compound ever marketed as a psychiatric drug? A. I beg your pardon.

Q. To your knowledge, was the dichloro compound ever sold or put into commerce? A. Sold?

Q. Sold or used by doctors for purposes of treating (145) patients with respect to psychiatric depression symptoms?

The Court: Is it used in psychiatry?

Mr. Ponack: The dichloro, was it marketed?

The Witness: I don't know.

By Mr. Armore:

Q. Has the monochloro compound been used? A. Yes. Now I am at the University Clinic in Basle and I know before I came to the clinic they used and at the moment use the monochloro compound; and I know the monochloro compound was used by Dr. Garrone in Geneva.

Q. Has the dichloro compound ever been used for that purpose? A. I have no idea.

Q. You don't know whether it has or not? A. No.

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(146) TESTIMONY OF DR. FELIX VON MENDELSSOHN

Direct Examination by Mr. Ponack:

Q. Dr. von Mendelssohn, may we have your full name,

Testimony of Dr. Felix von Mendelssohn—Direct.

Q. It is also a Schindler et al. but the monochloro is the compound which is here involved in issue. A. Right.

Q. On the basis of the results set forth in that affidavit, which I understand you have studied— A. Yes, I have.

Mr. Ponack: Sir?

The Court: I coughed.

Mr. Ponack: I am sorry.

By Mr. Ponack:

Q. How would you characterize the two test compounds from the standpoint of presence or absence of antidepressant utilities? A. From the records it is obvious, quite clear, that one drug, namely the dichloro, apparently is ineffective, whereas the monochloro drug has been very effective.

Q. Have you seen the Garrone affidavit which is of record in this case and is contained in plaintiffs' exhibit number 1, paper number 10? A. Yes, I have.

Q. What comment would you have there with respect (150) to confirming or negating the conclusion which you have just stated? A. Dr. Garrone had twenty-three cases of depressed patients, manic-depressive type, and in all twenty-three cases he had, from what he says, very good results with the monochloro drug.

Mr. Armore: I object, your Honor, to that line of testimony. It is completely hearsay.

Mr. Ponack: He didn't say he knows the work was done. He is evaluating it as an expert.

The Court: He is evaluating what appears there.

Mr. Ponack: That is right.

The Court: Go ahead.

Testimony of Dr. Felix von Mendelssohn—Direct.

By Mr. Ponack:

Q. Would you say that these affidavits show that the Schindler et al. compound, that is the patented dichloro compound, had the same utility—and I am quoting from the decision of the Board of Appeals:

“Said affidavits indicate that the Schindler et al. compound has the same utility as the claimed compound and differs therefrom merely in degree.”

What is your opinion with respect to what the Board of Appeals said about these affidavits? A. From the two papers I cannot share that opinion. I (151) think the two compounds are different. They must be different in kind because in all cases where the monochloride has been used it has been effective, and in the twenty-six cases where the dichloro has been used it has been ineffective.

* * * * *

Plaintiffs' Exhibit 1.

**Paper No. 1—Application of Schindler et al. Serial No.
857274 filed December 4, 1959, Specification as filed
and Claim 8.**

(See opposite ~~80~~)



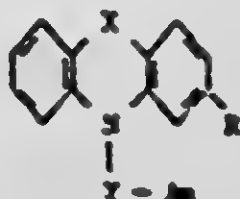
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New N-heterocyclic compounds

The present invention concerns new N-heterocyclic compounds having valuable pharmacological properties, as well as processes for the production thereof.

10,11-dihydro-5H-dibenzo[6,7]azepines and 5H-dibenz[6,7]azepines monoalkylated or halogenated in an aromatic ring as well as derivatives thereof have not been known up to now. It has now been found that N-derivatives of such compounds corresponding to the general formula



I

wherein X represents a member selected from the group consisting of the ethylene radical $-\text{CH}_2-\text{CH}_2-$ and the vinylene radical $-\text{CH}=\text{CH}-$,

R represents a member selected from the group consisting of the ethyl radical, the propyl radical, chlorine and bromine,

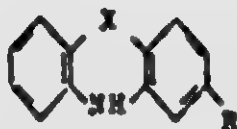
Y represents an alkylene radical with 2-3 carbon atoms, and

Am represents a member selected from the group consisting of a lower dialkylamino group, the pyrrolidino, piperidino, morpholino, N-ethyl-piperazino, N-hydroxyethyl-piperazino and N-methyl-piperidyl(2)- group,

5 have valuable pharmacological properties, in particular anti-
 allergic, sedative, spasmolytic, serotonin antagonistic, anti-
 10 emetic and adrenolytic activity; for example they also restrict
 the saliva secretions caused by pilocarpine. These substances
 can be administered perorally and, possibly, also subcutaneously
 among other purposes for the treatment of certain forms of mental
 disorders, in particular depressions, for the treatment of aller-
 15 gic rhinitis as well as to potentiate the action of other pharma-
 ceuticals, in particular, anaesthetics. Of the compounds accor-
 ding to the invention, the ones of particular value are those in
 which R in general formula I is chlorine.

Quaternary ammonium salts which are derived from the
 tertiary bases defined above have ganglioplegic activity.

15 The new compounds are produced by reacting a 3-alkyl- or 3-
 halogen- 10.11-dihydro-5H-dibenzo[5,6]azepine or a 3-alkyl- or
 3-halogen- 5H-dibenzo[5,6]azepine corresponding to the general
 formula



II

20 which in the following will be termed 3-alkyl- or 3-halogen-
 iminodibenzyls or 3-alkyl- or 3-halogen- iminostilbenes respective-
 ly, with a reactive ester of an amino alcohol of the general
 formula



III

wherein R, X, Y and Am have the meanings given above, the reaction being performed in the presence of a condensing agent.

Suitable condensing agents are, in particular, sodium amide, lithium amide, potassium amide, sodium or potassium, butyl lithium, phenyl lithium, sodium hydride or lithium hydride. The reaction can be performed in the presence or absence of an inert organic solvent, as examples of which can be named benzene, toluene and xylenes.

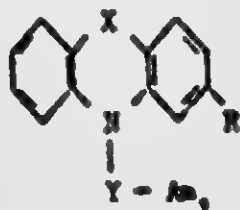
As reactive esters of amino alcohols of the general formula III, in particular the halides are used; individually can be named:

dimethylaminoethyl chloride, diethylaminoethyl chloride, methyl-ethylaminoethyl chloride, 3-dimethylamino propyl chloride, 3-dimethylamino-isopropyl chloride, γ -dimethylamino-propyl chloride, 3-(di-n-propylamino)-ethyl chloride, 3-(methyl-isopropylamino)-ethyl chloride, 3-(di-n-butylamino)-ethyl chloride, 3-(di-isobutylamino)-ethyl chloride, pyrrolidino-ethyl chloride, piperidino-ethyl chloride, γ -piperidino-propyl chloride, morpholino-ethyl chloride, 3-(N-methyl-piperizino)-ethyl chloride and N-methyl-piperidyl(2)-methyl chloride as well as the corresponding bromides and iodides.

Examples of starting materials of the general formula II which are suitable for the reaction are 3-ethyl-iminodibenzyl, 3-n-propyl-iminodibenzyl, 3-ethyl-iminostilbene, 3-chloro- and 3-bromo-iminodibenzyl and iminostilbene. The iminodibenzyl derivatives named above are obtained from unsubstituted iminodibenzyl

- dibenzyls or the corresponding iminostilbene derivatives are then obtained. These can be reacted, for example, with dimethylamino, methylethylamine, diethylamine, pyrrolidine, piperidine, morpholine, N-methyl-piperazine or N-hydroxyethyl-piperazine.

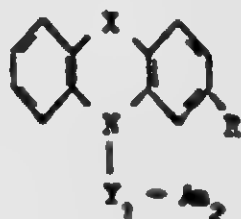
5 Compounds of the general formula I are obtained by a further process in which a compound of the general formula



VII

wherein AM_1 represents the primary amino group or a monoalkylamino group and X, R and Y have the meanings given above, is treated with a low molecular alkylating agent. Starting materials of the general formula VII are obtained, for example, if ammonia or a low molecular monoalkylamine is reacted analogously to the previous process instead of a secondary amine of the general formula VI, with a reactive ester of a compound of the general formula V or also if, for example, a 3-alkyl- or 3-halogen- 5-cyanoalkyl imino-dibenzyl or -iminostilbene is reduced or hydrogenated. Examples of low molecular alkylating agents are dimethyl sulphate, diethyl sulphate, methyl iodide, ethyl iodide, ethyl bromide, n-propyl bromide and p-toluene sulphonic acid methyl ester in the presence of acid binding agents such as, e.g. sodium or potassium carbonate, and of an inert organic solvent. Also, for example, formaldehyde in the presence of formic acid can be used.

Finally, compounds of the general formula I can also be produced by reacting compounds of the general formula



VIII

wherein Y_1 and Am_2 represent radicals corresponding to the definitions given for Y and Am above but in one of the two radicals, at least one methylene group bound to a nitrogen atom is replaced by a carbonyl group -CO-, and

X and R have the meanings given above,

with an alkali metal-earth metal hydride, in particular with lithium-aluminum hydride. This process is of importance particularly for the production of N'.N'-disubstituted 3-alkyl- or 3-halogen- 5-(α -aminomethyl-alkyl)-iminodibenzyls or -iminostilbenes because these compounds can be obtained, for example, by the first process only with the isomeric N'.N'-disubstituted 3-alkyl- or 3-halogen- 5-(β -aminoalkyl)-iminodibenzyls or -iminostilbenes formed by molecular rearrangement. The N'.N'-disubstituted 3-alkyl- or 3-halogen- 5-(α -carbonyl-alkyl)-iminodibenzyls or -iminostilbenes necessary for the production of the above compounds are obtained, for example, by reaction of alkali metal compounds of 3-alkyl- or 3-halogen- iminodibenzyls or -iminostilbenes of the general formula II with low molecular α -bromo-alkano carboxylic acid dialkylamides, pyrrolidides, piperidides, morpholides or 4-alkyl piperazides. Further starting materials of the general formula VIII are, for

example, the 3-alkyl- or 3-halogen- substituted 5-(dialkylamino alkanoyl)-, 5-(piperidino-alkanoyl)-, 5-(N'-alkyl-alkanoylamino-alkyl)-, 5-(N'.N'-dialkanoyl-aminoalkyl)-, 5-succinimidoalkyl- and 5-glutarimidoalkyl- iminodibenzyls and -iminostilbenes. The 5-dialkylaminoalkanoyl compounds are obtained, for example, by reacting alkali metal compounds of 3-alkyl- or 3-halogen iminodibenzyls or -iminostilbenes of the general formula II with halogen alkane carboxylic acid halides and then reacting the 5-halogen alkanoyl compounds obtained with suitable amines of the general formula VI. The other starting materials mentioned above are obtained, for example, by reacting reactive esters of compounds of the general formula V with alkali metal compounds of alkane carboxylic acid-N-alkylamides, succinimide or glutarimide, or by acylating 3-alkyl- or 3-halogen- 5-monoalkylaminoalkyl or 3-alkyl or 3-halogen- 5-aminoalkyl iminodibenzyls or iminostilbenes of the general formula VII.

Monoquaternary ammonium compounds are obtained from the tertiary amines of the general formula I in the usual way by adding reactive esters, in particular halides or sulphates of aliphatic or araliphatic alcohols, e.g. methyl iodide, dimethyl sulphate, ethyl bromide, ethyl iodide or benzyl chloride. In this addition the group Ar reacts.

The tertiary bases form salts, some of which are water soluble with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane disulphonic acid, acetic acid, citric acid, malic acid, succinic acid, fumaric acid, maleic acid, tartaric

acid, benzoic acid and phthalic acid.

P The following examples further illustrate the production of the new compounds. Parts are given therein as parts by weight, their relationship to parts by volume is as that of grammes to cubic centimetres. The temperatures are in degrees Centigrade.

Example 1

P 10 Parts of 3-ethyl-iminodibenzyl are dissolved in 50 parts by volume of anhydrous benzene and a solution of the base liberated from 9 parts of pyrrolidinoethyl chloride-hydrochloride in 150 parts by volume of anhydrous benzene is added. A suspension of 2.2 parts of sodium amide in toluene is added dropwise at 50° while stirring and then the reaction mixture is refluxed for 16 hours. It is then cooled and water is added. The benzene phase is separated and extracted with 2 N-hydrochloric acid; the hydrochloric acid extract is made alkaline with diluted caustic soda lye and extracted with ether. The ether solution is concentrated and the residue is distilled in a high vacuum whereupon the 3-ethyl-5-(3-pyrrolidino-ethyl)-iminodibenzyl passes over at 164° under 0.005 mm pressure. On treating with ethereal hydrogen chloride solution, the hydrochloride of the base named is obtained which, after recrystallisation from acetone/ether melts at 156-158°.

15 The same compound is obtained if the 3-ethyl-iminodibenzyl is reacted with pyrrolidino-ethyl bromide in the presence of lithium amide instead of with pyrrolidino-ethyl chloride in the presence of sodium amide.

i In an analogous manner, on using the base liberated from 8 parts of dimethylaminoethyl chloride-hydrochloride, 3-ethyl-5-(3-dimethylamino-ethyl)-iminodibenzyl (3.7.0.005 145-147°) is obtained and on using 7 parts of 1-(N-methyl-piperazino)-propyl chloride, 3-ethyl-5-(1-(N-methyl-piperazino)-propyl)-iminodibenzyl (R.P. 0.004 183-184°) is obtained, the dihydrochloride of which

6 ~~Melts at 236-240° on decomposition.~~

Also in an analogous manner, starting from 10.7 parts of 3-n-propyl-iminodibenzyl and the base liberated from 8.5 parts of γ -dimethylaminopropyl chloride-hydrochloride, 3-n-propyl-5-(γ -dimethylamino-propyl)-iminodibenzyl B.P. 0.001 142-144° is obtained and also, starting from 9.9 parts of 3-ethyl-iminostilbene and the base liberated from 8.5 parts of γ -dimethylaminopropyl chloride-hydrochloride, 3-ethyl-5-(γ -dimethylamino-propyl)-iminostilbene B.P. 0.004 152° is obtained.

Example 2

22.9 Parts of 3-chloro-iminodibenzyl are dissolved in 300 parts by volume of xylene and 4 parts of sodium amide, pulverised and suspended in toluene, are added while stirring in a nitrogen atmosphere. The xylene solution immediately becomes dark coloured but on the sodium salt crystallising out it becomes light coloured again. The reaction mixture is stirred for about 2 hours at 80° until the development of ammonia has ended. A solution of γ -dimethylamino-propyl chloride (liberated from 17.4 parts of hydrochloride with caustic soda lye, i.e. about 10% excess, taken up in toluene and dried for 2 hours with anhydrous sodium sulphate),
to the sodium salt
in toluene is added/and the whole is stirred under reflux for 15 hours. The precipitated sodium chloride is filtered off and the filtrate is concentrated. The residue is diluted with ether, and the hydrochloride of 5-(γ -dimethylaminopropyl)-3-chloro-iminodibenzyl is precipitated by introducing anhydrous hydrochloric acid. It is filtered off under suction and purified by repeated recryst-

tallisation from acetone whereupon it melts at 191.5 - 192°.

In an analogous manner, on using the base liberated from 17.4 parts of γ -diethylamino-propyl chloride-hydrochloride^e 5-(γ -diethylaminopropyl)-3-chloro-iminodibenzyl is obtained, and on using the base liberated from 20.5 parts of β -piperidino-ethyl chloride-hydrochloride, 5-(β -piperidino-ethyl)-3-chloro-iminodibenzyl is obtained. On the other hand, starting from 27.4 parts of 3-bromo-iminodibenzyl, 5-(γ -dimethylamino-propyl)-3-bromo-iminodibenzyl is obtained analogously to the above example.

Example 3

23 Parts of 3-chloro-iminodibenzyl are dissolved in 190 parts by volume of xylene, 4.3 parts of sodium amide, pulverised and suspended in toluene, are added and the whole is stirred for 3 hours at 80° in a nitrogen atmosphere. The solution becomes dark coloured at first but lightens as soon as the sodium salt begins to crystallise. The morpholino-ethyl chloride solution (liberated from 20.5 parts of hydrochloride with diluted caustic soda lye and taken up in benzene) is added to the sodium salt. The reaction mixture is then refluxed for 16 hours while continuously stirring. After concentrating and cooling, the precipitated sodium chloride is filtered off and washed with anhydrous ether. Anhydrous hydrochloric acid gas is introduced into the solution in the cold. The hydrochloride of 3-chloro-5-(β -morpholino-ethyl)iminodibenzyl is filtered off under suction and recrystallised from alcohol. It melts at 242°.

Example 4

23 parts of 3-chloro-iminodibenzyl are dissolved in 190 parts by volume of xylene, 4.3 parts of sodium amide (pulverised and suspended in toluene) are added and the whole is stirred for 3 hours at 80° in a nitrogen atmosphere. The dimethylaminoisopropyl chloride (liberated from 18 parts of hydrochloride of dimethylamino-isopropyl chloride with diluted caustic soda lye and taken up in benzene, the benzene solution dried for 2 hours with anhydrous sodium sulphate) is then added and the reaction mixture is refluxed for 16 hours while stirring. The precipitated sodium chloride is filtered off, washed with anhydrous ether and the hydrochloride of the 3-chloro-5-(3-dimethylamino-^{isopropyl}~~isopropyl~~-1-ethyl)-iminodibenzyl is precipitated from the filtrate by the introduction of anhydrous hydrogen chloride. It is recrystallised from a great deal of acetone and in the pure state melts at 247°.

Example 5

8 Parts of pyrrolidine are added to a solution of 15 parts of 3-ethyl-5(3-chloroethyl)-iminodibenzyl in 100 parts by volume of anhydrous benzene and the whole is refluxed for 12 hours. After cooling, the benzene solution is thoroughly washed with water, dried and concentrated. The calculated amount of anhydrous alcoholic hydrochloric acid is added to the residue whereupon the hydrochloride of 3-ethyl-5-(3-pyrrolidino-ethyl)-iminodibenzyl crystallises out. It can be recrystallised as described in example 1 and then melts at 156-158°.

Example 6

2 10 Parts of 3-n-propyl-5-(γ-methylamino-propyl)-iminodibenzyl are dissolved in 7.0 parts by volume of 85% formic acid and 4.5 parts by volume of 30% formalin are added to the solution.
5 The whole is left to stand for 3 hours at room temperature and is then heated for 12 hours on a steam bath. After cooling, the reaction mixture is concentrated in the vacuum, the residue is made alkaline with 30% caustic soda lye and the whole is extracted with ether. After washing and drying, the ether extracts are
10 concentrated and the residue is distilled whereupon the 3-n-propyl-5-(γ-dimethylamino-propyl)-iminodibenzyl is obtained, B.P. 0.001 - 142-144°.

Example 7

15 23 Parts of 3-chloro-iminodibenzyl and 15 parts of 1-chloro-3-bromo-propane are dissolved in 200 parts by volume of anhydrous benzene. 4.3 Parts of sodium amide, pulverised and suspended in toluene, are slowly added dropwise while stirring at 50° and the stirring is then continued for 15 hours at 50-60°. The
20 reaction mixture obtained is poured into water, the benzene phase is separated and dried with sodium sulphate. After concentrating, 3-chloro-5-(γ-chloro-propyl)-iminodibenzyl is obtained as a dark oil which can be further worked up direct.

P. A.
25 ~~23 Parts of the product obtained above are dissolved in 150 parts by volume of methyl ethyl ketone, 10 parts of sodium iodide and 13 parts of N-methyl-piperazine are added and the whole is stirred under reflux for 16 hours. The reaction mixture is~~

2
3
4
5
concentrated, the residue is dissolved in ether and the basic portions are extracted with diluted hydrochloric acid from the ethereal solution. The acid extracts are made alkaline and the precipitated base is dissolved in ether. After drying and concentrating the solution, the desired 3-chloro-5- γ -(N'-methyl-piperazino)-propyl-7-iminodibenzyl is obtained as an oil.

3-Chloro-5- γ -(N'-hydroxyethyl-piperazino)-propyl-7-iminodibenzyl is obtained in an analogous manner on using, for example, N-hydroxyethyl-piperazine instead of N-methyl-piperazine.

10 Example 8

15
20
23 Parts of 3-chloro-iminodibenzyl are dissolved in 150 parts by vol. of anhydrous xylene and 4.3 parts of sodium amide, pulverised and suspended in toluene, are added. The mixture is stirred and heated to 90° whereupon ammonia is developed and the sodium salt is formed. β -N-methyl-piperidyl(2')-ethyl chloride (liberated from 22 parts of the hydrochloride and taken up in toluene) is added to the suspension of the sodium salt obtained and the whole is refluxed for 16 hours. After cooling, the precipitated sodium chloride is separated, the solution is concentrated and the oil is distilled at 0.1 mm pressure. The 3-chloro-5- γ -(N'-methyl-piperidyl(2'))-ethyl-7-iminodibenzyl passes over at 195°.

25 Example 9

23 Parts of 3-chloro-iminostilbene dissolved in 250 parts by volume of anhydrous xylene, to which 4.3 parts of sodium amide, pulverised and suspended in toluene, are added are refluxed for 3 hours. γ -Dimethylamino-propyl chloride (liberated from 18 parts of the hydrochloride and taken up in xylene) is added and the whole

is refluxed for 20 hours while stirring. The reaction mixture
2 obtained is evaporated to dryness, ether is added to the residue
and the basic portions are extracted from the ethereal solution
with diluted hydrochloric acid. The acid extracts are made
5 alkaline and the free base is dissolved in ether. After drying
and concentrating the ether solution, the desired 3-chloro-5-
(γ-dimethylamino-propyl)-iminostilbene is obtained. Recrystallized
from petroleum ether it melts at 53°.

Claim 8. 3-Chloro-5-(γ-dimethylamino-propyl)-iminodibenzyl.

Plaintiffs' Exhibit 1.

*Plaintiffs' Exhibit 1.***Paper No. 2—Official Letter of July 14, 1960.****U. S. DEPARTMENT OF COMMERCE
PATENT OFFICE
Washington**

* * * * *

This application has been examined.

References cited:

Schindler et al	2,813,857	Nov. 19, 1957	260/239
Austrian Patent (4 pages)	200,578	Nov. 10, 1958	260/239
Australian Patent (5 pages)	215,335	June 11, 1958	260/268

* * * * *

Claims 1-4, 6 and 8-13 are rejected as being unpatentable over Schindler et al alone or in view of the Australian patent. Schindler et al discloses 3, 7-dihalo-5-tertiary amino alkyl-iminodibenzyl compounds having pharmacological properties. The Australian patent discloses in the analogous iminodibenzyl compounds in which the tertiary amino group is a piperazine that 3, 7-dihalo, 3-halo, and 3-alkyl substituents are equivalent. In view of such teaching, no invention is seen in the 2-halo or 3-alkyl compounds over the 3, 7 dihalo compounds of the Schindler et al patent. In addition, no invention is seen in the mono halo compounds over the dihalo compounds of the Schindler et al reference alone since the mono halo compounds would be expected to exhibit analogous properties.

* * * * *

Plaintiffs' Exhibit 1.

Paper No. 3—Amendment filed January 13, 1961.

Mail Room

Jan 13 1961

U. S. Patent Office

IN THE UNITED STATES PATENT OFFICE

In re application of

WALTER SCHINDLER and

HENRI DIETRICH

Div. 6

Serial No. 857,274

Room 4733

Filed December 4, 1959

New N-heterocyclic Compounds

Hon. Commissioner of Patents,
Washington, D. C.

Sir:

In response to the Official action of July 14, 1960, kindly
amend the above entitled application as follows:

• • • • •

REMARKS

Favorable reconsideration of the present application is
respectfully requested in view of the foregoing changes
and the following representations.

• • • • •

The rejection of claims 1, 3, 4, 6 and 8 to 13 as allegedly
unpatentable over Schindler et al. alone or in view of the
Australian patent is also controverted. The primary refer-
ence relates exclusively to dichloro-iminodibenzyls. In
contrast, the instant claims are directed to (*monoethyl-,*
monopropyl-, monochloro- and monobromo-)5-aminoalkyl-
iminodibenzyls and corresponding stilbene compounds. The

Plaintiffs' Exhibit 1.

Examiner asserts that the monohalo compounds "would be expected to exhibit analogous properties" as compared to the dihalo compounds. The basis for this assertion is not evident in the record, and the Examiner is invited to cite basis for the assertion. The fact is that the properties of the monohalo and dihalo compounds are considerably different. It can be shown for example that the spasmolytic activity of the claimed monochloro compounds, as to the acetyl choline test, is significantly superior to that of the dichloro compounds. The Examiner states that the Australian patent discloses in the analogous iminodibenzyl compounds, in which the tertiary amino group is a piperazine, that 3, 7-dihalo, 3-halo and 3-alkyl substituents are equivalent. The Australian patent is limited to piperazino-containing compounds. Furthermore there is no teaching in the Australian patent of any preferred position, e.g. 3,7 or 3. Moreover even if it is conceded (*only* for argumentative purposes) that the Australian reference showed compounds having the 3,7-dihalo, 3-halo, and 3-alkyl as equivalent, the teaching of the instant specification is exactly to the contrary. The applicants' claims are limited to monosubstituted compounds and as can be noted from preceding comments on the Schindler et al reference, monosubstituent compounds are *not* equivalent to disubstituted compounds. The Examiner has included in the instant rejection claims 3, 4 and 6. There is no reference to a propyl or ethyl moiety in the Australian reference and it is difficult to see the Examiner's basis for his position.

Summing up, there appears to be no tenable basis for the Examiner's combination of the Australian reference with Schindler. The Australian reference is drawn exclusively to piperazino compounds and is further vague and indefinite as to what Y and Y₁ are, nor where they are in the molecule in question. The appurtenant rejection therefore fails and should be withdrawn.

• • • • •

Plaintiffs' Exhibit 1.

Paper No. 4—Official Letter of July 3, 1961.

**U. S. DEPARTMENT OF COMMERCE
PATENT OFFICE
Washington**

• • • • •

Claims 1, 2, 4, 6 and 8-13 are again rejected as being unpatentable over Schindler et al alone or in view of the Australian patent for reasons of record in paper no. 2, page 2. Applicants' arguments have been carefully considered but are not deemed persuasive. In view of the disclosure of the Australian patent that "Y and Y₁ are the same or different and are selected from hydrogen atoms, halogen atoms and lower alkyl, lower alkoxy, aryl and aryloxy", no invention is seen in applying this teaching to the closely analogous compounds of Schindler et al as the compounds resulting therefrom would be obvious.

• • • • •

All the claims are rejected.

An issue having been reached, this rejection is hereby made FINAL.

• • • • •

Plaintiffs' Exhibit 1.

Paper No. 5—Amendment filed January 3, 1962.

U. S. Patent Office
Mailroom
Jan 3 1962

IN THE UNITED STATES PATENT OFFICE

In re application of
WALTER SCHINDLER ET AL
Serial No. 857,274
Filed December 4, 1959
New N-Heterocyclic Compounds

Div. 6.
Room 4733

Hon. Commissioner of Patents,
Washington, D. C.

Sir:

.

REMARKS

Further and favorable reconsideration is respectfully requested in view of the foregoing changes, the accompanying showings and the following representations.

.

The rejection of claims 1, 2, 4, 6, and 8 to 13 on Schindler et al alone or in view of the Australian patent is also respectfully traversed. Here again, the applicants rely *in toto* on the appurtenant remarks made on pages 6 (bottom) and 7 of the amendment of January 13, 1961, to which the Examiner is respectfully referred. Note that the Examiner has not responded to the applicants' invitation for support for his holding that the monohalo compounds would be expected to exhibit analogous properties to those of the dihalo compounds.

The Schindler et al patent in no uncertain terms is directed to dihalogen containing compounds; cf. col. 1, lines 25-37. Even if one were to concede—solely arguendo—that

Plaintiffs' Exhibit 1.

the Examiner's attempted combination with the Australian patent is permissible, the end result equates the dichloro compound of Schindler et al with the Examiner's postulated monochloro compound. That, as has been asserted by the applicants of record, there actually is no such equivalence established by the second affidavit (B) filed herewith; note monochloro compound 1 and the corresponding dichloro compound 2. Note also the monochloro compound 3 vs. the corresponding dichloro compound 4. The results set forth on pages 3 and 4 of this affidavit establish in no uncertain terms, the non-equivalency of the two types of compounds; moreover, the affidavit confirms the superiority of the monochloro compounds in comparison with the dichloro compounds.

The foregoing makes the assumption, arguendo, that the Examiner has a valid basis for his attempted combination. Actually, however, the secondary reference, i.e. the Australian patent, has not been properly combined with the Schindler et al patent. The Australian patent is *restricted* to *piperazino* compounds only and such have been shown to be *non-equivalent* to compounds of the instant application. Hence since the amino moiety of the compounds of the secondary reference is non-equivalent to the amino moiety of the primary reference as shown by the affidavit (A), irrespective of the fact that the primary reference is drawn exclusively to dihalogeno compounds, the Examiner has no basis for taking a moiety of the secondary reference and substituting it for a moiety of the primary reference. It is not seen where there is anything in the references on record that would suggest the superiority as substantiated by the affidavit of the claimed compounds in question over the dihalo compounds and hence make the claimed compounds "obvious" as the Examiner has alleged.

Accordingly, the rejection based on Schindler et al alone or in view of the Australian patent fails and should be withdrawn.

• • • • • •

Plaintiffs' Exhibit 1.

Paper No. 6—Notice of Appeal.

MAIL ROOM
JAN 3, '62
U. S. PATENT OFFICE

BOARD OF APPEALS
JAN 10, 1962
U. S. PATENT OFFICE

APPEAL No. 34 57

**IN THE UNITED STATES PATENT OFFICE
APPEAL TO THE HONORABLE BOARD OF APPEALS**

In re application of
WALTER SCHINDLER et al
Serial No. 857,274
Filed December 4, 1959
New N-Heterocyclic Compounds

Div. 6
Room 4733

Hon. Commissioner of Patents
Washington, D. C.

Sir:

Applicants hereby appeal to the Board of Appeals from the decision of the Principal Examiner dated July 3, 1961, finally rejecting claims 1, 3, 4, 6 to 13 inclusive and 16 and 17.

An oral hearing is requested.

Respectfully submitted,

WALTER SCHINDLER et al
By WENDEROTH, LIND & PONACK
Attorneys
Per A. PONACK

Washington, D. C.
January 3, 1962.

Paper No. 6—Affidavit "A" of Dr. H. Wirz.

(See opposite )

Schindler et al.

Division 6

Case 1214/80
December, 1961

Ser. No. 857,274
Filed December 4, 1959

New N-Heterocyclic Compounds

A F F I D A V I T

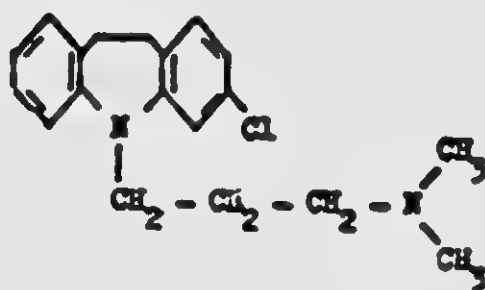
I, Heinrich Wirz, doctor of the University of Basle, Switzerland, physician and physiologist, Professor extraordinarius of Physiology in the University of Basle, a citizen of the Swiss Confederation and resident of Riehen near Basle, Switzerland, being duly sworn, make the following declarations:

In view of Paper No. 4 issued in the matter of the above entitled patent application on the 3rd of July 1961 I have been asked by one of the inventors of the subject matter of the above mentioned application, Ser. No. 857,274 to make some tests in connection with comparing the spasmolytic (atropine-like) activity and antagonistic action to serotonin of compounds according to Ser. No. 857,274 against corresponding piperazino compounds.

Tests having now been made and achieved under my direction I beg to submit herewith an exact report about how the same were carried out.

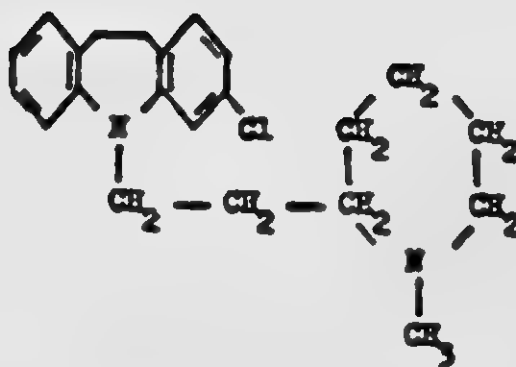
I Compounds tested:

1.



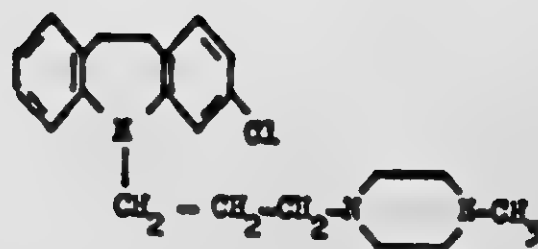
according to the present application

2.



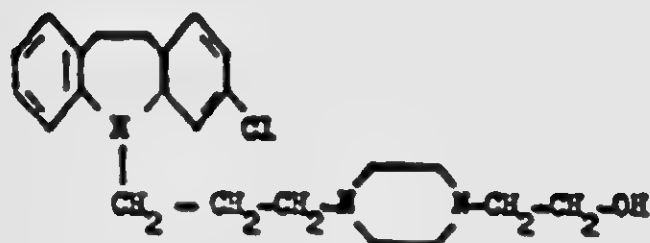
according to the present application

3.



analogous piperazine compound

4.



analogous
riponazine compound

Spasmolytic (atropine-like) activity:

a) Method:

Surviving intestine of guinea pig (according to Magnus) in a tyrode solution was brought by means of acetylcholine into a contracted state and the doses of the substances to be tested which have the same contraction releasing action as 1 γ of atropine applied on the same intestine were ascertained.

b) Results:

Compound	Doses in γ giving the same contraction releasing effect as 1 γ of atropine
----------	--

1.	14
2.	4
3.	51
4.	102

III Antagonistic action to serotonin:

c) Method:

The serotonin-antagonistic action of the test substances was evaluated by determining their inhibiting action on the formation of oedema following injection of an aqueous solution of the creatinin-sulphate of serotonin (3-(β -amino-

ethyl)-5-hydroxyindole) into rats hind paws. The tests were carried out as follows:

Substances to be tested were injected in the form of an aqueous solution of its hydrochloride, intraperitoneally into an albino rat. Each substance was administered to a series of 18 rats. After five minutes 0.1 ml of an aqueous solution containing serotonin creatinin sulphate in a concentration corresponding to 500 γ of serotonin salt in 1 ml water were injected into one hind paw of each rat. Control series of 18-27 rats which had not received any test substance were treated in the same way with serotonin solution. The average weight of the animals used in the different series was about 130 g. After 2 hours the animals were sacrificed, both hind paws were amputated and the extent of swelling was determined by comparing the weights of the paws treated with serotonin solution and the untreated paws. From the average differences between both paws in the test series and in the control series, the reduction of swelling due to the administration of the substances to be tested was calculated in percent of the swelling in the control series.

d) Results:

Compound	dosis in mg/kg	reduction of swelling
1	25	51%
	10	50%
2	25	61%
	10	39%
3	25	6%
4	25	11%

IV Toxicity

e) Method:

The dosis letalis 50 (LD 50) was determined as follows:
The substances to be tested were injected intravenously in the form of aqueous solutions of their hydrochlorides to albino mice in different single doses. For each dose 5-25 animals were used, their weights being about 20 g. The animals were observed for one week after the administration of the substances.

The LD 50 was determined by graphic interpolation from two doses actually administered, one of which killed less than half and the other more than half the number of animals treated (Schleicher and Schull probability graph paper 298 1/2 was used for the graphic interpolation).

f) Results:

Compound	Dosis letalis 50 mice i.v. in mg/kg body weight
1	45
2	45
3	49
4	91

V Conclusions

Compounds 1 and 2 according to Ser. No. 857,274 filed December 4, 1959 have a superior spasmolytic activity and antagonistic action to serotonin in comparison with corresponding piperazino compounds. The toxicity of compounds 1 to 3 are about equivalent. Compound 4 has a lower toxicity. However, a more than seven-fold increase in dose of compound 4 is required to give the same spasmolytic activity as compounds 1 and 2. Moreover, a 2 1/2 times increase in dose level of compound 4 (thus cancelling the toxicity difference) produces less than 1/3 the antagonistic action to serotonin of compounds 1 and 2.

And I make these declarations sincerely.

Heinrich Wieg

Consulate of the United States of America
San Francisco, California

Subscribed and sworn to before me this 15th
day of December 1961

02553
Serial No. 40
Fee Paid: U.S. \$ 2.50
Serial No. 1162

Russell O. Pickett
Russell O. Pickett
Vice Consul of the
United States of America

Plaintiffs' Exhibit 1.

Plaintiffs' Exhibit 1.

Paper No. 6—Affidavit "B" of Dr. H. Wirz.

(See opposite **100**)

Ser. No. 857,274
Filed December 4, 1959

New N-Heterocyclic Compounds

A F F I D A V I T

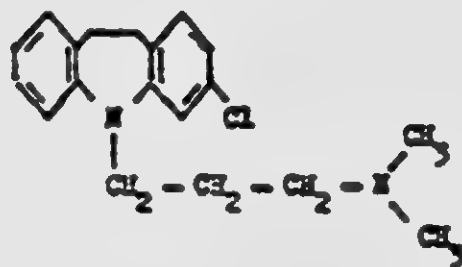
I, Heinrich Wirz, doctor of the University of Basle, Switzerland, physician and physiologist, Professor extraordinarius of Physiology in the University of Basle, a citizen of the Swiss Confederation and resident of Richon near Basle, Switzerland, being duly sworn, make the following declarations:

In view of Paper No. 4 issued in the matter of the above entitled patent application on the 3rd of July 1961 I have been asked by one of the inventors of the subject matter of the above mentioned application, Ser. No. 857,274 to make some tests in connection with comparing the spasmolytic (atropine-like) activity and antagonistic action to serotonin of compounds according to Ser. No. 857,274 against compounds according to U.S. Patent No. 2813,857 and Ser. No. 822,185 filed June 23, 1959.

Tests having now been made and achieved under my direction I beg to submit herewith an exact report about how the same were carried out.

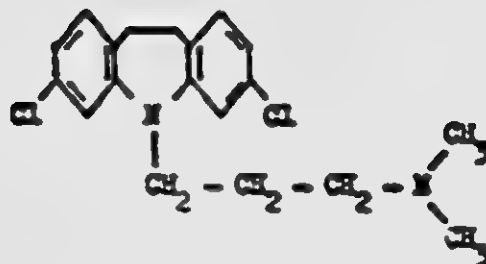
I Compounds tested:

1.



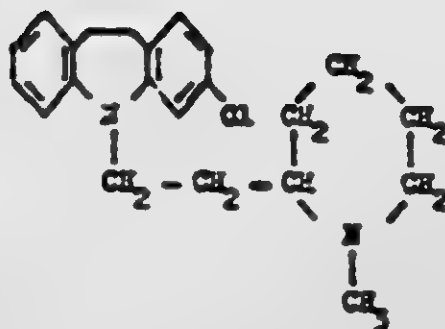
according to the
present application

2.



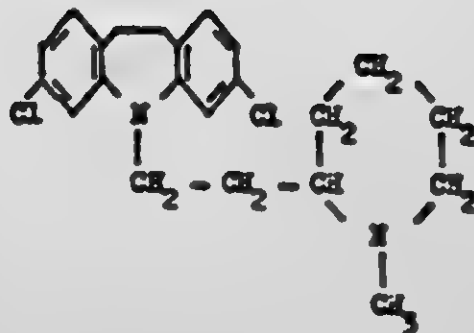
according to
USP 2,813,957

3.



according to the
present application

4.



according to
application
Serial No. 822,185

II Spasmolytic (atropine-like) activity

a) Method:

Surviving intestine of guinea pig (according to Magnus) in a tyrode solution was brought by means of acetylcholine into a contracted state and the doses of the substances to be tested which have the same contraction releasing action as 1 γ of atropine applied on the same intestine were ascertained.

b) Results:

Compound No.	Doses in γ giving the same contraction releasing effect as 1 γ of atropine
--------------	--

1.	14
2.	92
3.	4
4.	51

III Antagonistic action to serotonin:

c) Method:

The serotonin-antagonistic action of the test substances was evaluated by determining their inhibiting action on the formation of oedema following injection of an aqueous solution of the creatinin-sulphate of serotonin (3-(β -amino-ethyl)-5-hydroxyindole) into rats hind paws. The tests were carried out as follows:

Substances to be tested were injected in the form of an aqueous solution of its hydrochloride, intraperitoneally into an albino rat. Each substance was administered to a series of 18 rats. After five minutes 0.1 ml of an aqueous solution containing serotonin creatinin sulphate

in a concentration corresponding to 500 γ of serotonin salt in 1 ml water were injected into one hind paw of each rat. Control series of 18-27 rats which had not received any test substance were treated in the same way with serotonin solution. The average weight of the animals used in the different series was about 130 g. After 2 hours the animals were sacrificed, both hind paws were amputated and the extent of swelling was determined by comparing the weights of the paws treated with serotonin solution and the untreated paws. From the average differences between both paws in the test series and in the control series, the reduction of swelling due to the administration of the substances to be tested was calculated in percent of the swelling in the control series.

d) Results:

Compound	dosis in mg/kg	reduction of swelling
1	25	51%
	10	50%
2	25	31%
	10	2%
3	25	62%
	10	37%
4	25	30%
	10	20%

IV Toxicity

e) Methods:

The dosis letalis 50 (LD 50) was determined as follows:
The substances to be tested were injected intravenously in the form of aqueous solutions of their hydrochlorides

to albino mice in different single doses. For each dose 5-25 animals were used, their weights being about 20 g. The animals were observed for one week after the administration of the substances.

The LD 50 was determined by graphic interpolation from two doses actually administered, one of which killed less than half and the other more than half the number of animals treated (Schleicher and Schull probability graph paper 298 1/2 was used for the graphic interpolation).

f) Results:

Compound	Dosis letalis 50 mice i.v. in mg/kg body weight
1	45
2	42
3	45
4	45

Y Conclusions:

Compounds 1 and 3 according to Ser. No. 857,274 filed December 4, 1959 have a superior spasmolytic activity and antagonistic action to serotonin, than compounds 2 and 4 according to U.S. Patent 2,813,857 and Ser. No. 822,185 respectively.

It should be noted that compound 1 has more than a six-fold spasmolytic (atropine-like) activity in comparison with the corresponding dichloro compound 2. Likewise compound 3 has more than a 12-fold spasmolytic activity in comparison with the corresponding dichloro compound 4. Compounds 2 and 4 in the higher dose (2.5 times greater than the lower dose of compounds 1 and 3) are considerably less active than the lower dose of compounds 1 and 3 with respect to the antagonistic action to serotonin. The toxicity of the four compounds in question is practically the same.

And I make these declarations sincerely.

Henrich Wey

Notary Public
City of New York
State of New York

Subscribed and sworn to before me this 15th
day of December 1961

02552
Serial No. 49
For Fed: U.S. 250
State No. 1166

Russell O. Prickett
Russell O. Prickett
Vice Consul of the
United States of America

Plaintiffs' Exhibit 1.

Plaintiffs' Exhibit 1.

Paper No. 7—Official Letter of January 30, 1962.

**U. S. DEPARTMENT OF COMMERCE
PATENT OFFICE
Washington**

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Responsive to amendment filed January 3, 1962.

The amendment has been considered and will be entered for purposes of appeal since it places the case in better condition for appeal.

The amendment and affidavits presented fail to place the case in condition for allowance for reasons set forth below.

• • • • •

The rejection of claims 1, 4, 6, 8 and 11 as being unpatentable over Schindler et al alone or in view of the Australian patent is deemed sound and is maintained. In view of the references cited the claimed mono-substituted compounds would be obvious to one skilled in the art, as compounds.

• • • • •

This application has been returned to the Board of Appeals to await applicants' perfection of the appeal.

• • • • •

Plaintiffs' Exhibit 1.

Paper No. 10—Letter filed March 7, 1962.

BOARD OF APPEALS
MAR 7, 1962
U. S. PATENT OFFICE

IN THE UNITED STATES PATENT OFFICE

In re application of

WALTER SCHEINDLER ET AL

Serial No. 857,274

Div. 6

Filed December 4, 1959

Room 4733

NEW N-HETEROCYCLIC COMPOUNDS

Honorable Commissioner of Patents,
Washington, D.C.

Sir:

Supplementing the response of January 3, 1962, the applicants submit herewith two further affidavits directed more especially to the compound of claim 8 and which, it is submitted, unequivocally establish the allowability of the said claim.

The first of these affidavits confirms the record assertion of the anti-depressive utility of the new compounds of the invention. Note the assertion by the affiant, Dr. Garrone, that the therapeutic (anti-depressive) effect of the compound of claim 8 "manifests itself faster than that of any other known thymolepticum" and that it results in "marked improvement" in the case of patients suffering from depression.

The second affidavit—that by Dr. Pöldinger—is concerned more especially with a comparison of the therapeutic action of the compound of claim 8 (3-chloro-5-

Plaintiffs' Exhibit 1.

(γ -dimethylaminopropyl)-iminodibenzyl) relative to the known 3,7-dichloro-5-(γ -dimethylaminopropyl)-iminodibenzyl. The showing clearly establishes that, with respect to depressed patients, the latter gives "little or no relief" while a satisfactory improvement was achieved with the compound according to the present application.

The foregoing negates—certainly in respect of claim 8—the Examiner's holding of unpatentability over Schindler et al alone and, by the same token, over such patent in view of the Australian patent.

The Examiner does not deny the novel character of the claimed compounds. It is wholly incomprehensible that those skilled in the art working in the same field—here the prior patentees—would have overlooked the new compounds (e.g. the compound of claim 8), if the latter were indeed as "obvious" from the prior patents as the Examiner would appear to believe.

The showings here submitted manifestly involved a considerable amount of time-consuming work which explains why it has not been possible to present such showings at an earlier date.

The Examiner is requested to review the situation in the light of such showings and to take the further appropriate action looking toward the issuance of a Notice of Allowance in this case.

Respectfully submitted,

WALTER SCHINDLER et al.

By WENDEROTH, LIND & PONACK
Attorneys

Per A. PONACK

Washington, D.C.
March 7, 1962

Paper No. 10—Affidavit of Dr. W. Poldinger.

(See opposite )

MAR 7 - 1962

U. S. PATENT OFFICE

Schindler et al.

Division 6

Case 1214/60
February, 1962

Ser. No. 857,274
Filed December 4, 1959

New N-Heterocyclic Compounds

A F F I D A V I T

I, Walter Püldinger, a citizen of Austria and resident of St. Urban, Luzern, Switzerland, being duly sworn, make the following declarations:

In 1953, I received my Doctorate in Medicine from the University of Vienna, Austria. I am a specialist in psychiatry and a member of the Austrian Society of Physicians and of the Austrian Electroencephalographic Society. I have been at the cantonal psychiatric clinic at St. Urban, Luzern, Switzerland, for approximately five years and am presently chief of the psychopharmacological department. I have published fifteen papers in the field of psychiatry, some of which are enumerated below: (titles translated from German)

1. Comparative Clinical Experiences Employing Psychopharmaceuticals With Psychiatric Patients Having Varied Disturbances -
Therapeutische Umschau 16, 245 (1959)
2. A Neurolyptic With Anti-Depressive Action, "Taractan" -
Praxis, 40, 463 (1960)
3. Tranquillizers -
Therapeutische Umschau 17, 200 (1960)
4. Predominately Anti-Depressively Effective Psychopharmaceuticals With Psychiatric Indications -
Helvetica Med. Acta. 28, 572 (1961)
5. Therapeutic Experiences With Thiopropazat and With a Combination of Thiopropazat with Chlorophencyclan (Vesitan) in Psychiatry -
Praxis 51, 73 (1962)
6. Clinical Experiences With the Iminostilbene Derivative G 33040 -
Therapeutische Umschau 19, 34 (1962)

In view of Paper No. 4 issued in the matter of the above entitled patent application on the 3rd of July 1961 I have been asked by the inventors of the subject matter of the above application, Ser. No. 857,274 to report on some clinical tests in connection with comparing the therapeutical action of 3-chloro-5-(γ -dimethylaminopropyl)-iminodibenzyl according to Ser. No. 857,274 (claim 8) against 3,7-dichloro-5-(γ -dimethylaminopropyl)-iminodibenzyl according to U.S.P. 2,813,857.

Tests having been made and achieved under my direction I beg to submit an exact report about how same were carried out.

Clinical investigation of 3,7-dichloro-5-(γ -dimethylamino-propyl)-iminodibenzyl

Ten persons suffering from severe endogenous depression and sixteen persons suffering from severe schizophrenia were hospitalized at the cantonal psychiatric clinic St. Urban, Luzern, Switzerland and treated either intramuscularly or perorally with 3,7-dichloro-5-(γ -dimethylaminopropyl)-iminodibenzyl in the form of injections of 25 mg/5 ml or tablets of 25 mg respectively. The persons treated comprised four age groups, i.e.

Group	Age
II	21-35
III	36-50
IV	51-65
V	66-

The following is a report of the cases:

a) Endogenous depression

Case No.	Age	Predominant Symptoms	Injection	Dosage tablets	Duration of treatment	Drive	Effect Mood	Others
1 ♂	III	depressive mood	3x1 3x2		3 days 2 days	no change	questionable	no change
2 ♂	III	Inhibition	3x1 3x2		3 days 3 days	no change	no change	no change
3 ♂	II	Inhibition	3x1		5 days	no change	no change	no change
4 ♂	IV	depressive mood	3x1		10 days	no change	questionable	no change
5 ♂	III	Inhibition		3x2	5 days	no change	no change	no change
6 ♂	III	depressive mood		3x1 3x2	4 days 6 days	worse	much worse	General condition growing worse
7 ♂	II	depressive mood		3x1	10 days	much worse	much worse	General condition growing worse
8 ♂	III	depressive mood		3x2 3x3	3 days 4 days	worse	much worse	General condition growing worse
9 ♂	IV	agitation	3x1		4 days	no change	no change	minimum sedation
10 ♂	III	Inhibition	3x1		3 days	no change	no change	sedation

b) Schizophrenia

Case No.	Age	Predominant Symptoms	Injection	Dosage tablets	Duration of treatment	Drive	Effect on Mood	Others
11-17 ♂	11-14	depressive mood and inhibition		3x1 to 3x2	3-14 days	no change	no change	no change
18-20 ♂	11-13	as case 11-17	3x1	3x1	4 days 6-10 days	no change	no change	no change
21 ♂	III	as case 11-17		3x1	6 days	no change	no change	General condition growing worse
22 ♂	II	as case 11-17		3x1	6 days	no change	no change	General condition growing worse
23 ♂	III	depressive mood		3x2	3 weeks	worse	worse	
24 ♂	III	depressive mood		3x1	2 weeks	worse	worse	
25 ♂	III	depressive mood		3x1 3x2	3 days 4 days	worse	worse	General condition growing worse
26 ♂	IV	depressive mood		3x2	20 days	worse	worse	General condition growing worse

B. Clinical investigation of 3-chloro-5-(γ -dimethylaminopropyl)-iminodibenzyl

Seven persons hospitalized at the cantonal psychiatric clinic, St. Urban, Luzern, Switzerland for severe mental disorders were treated either intramuscularly or perorally with 3-chloro-5-(γ -dimethylaminopropyl)-iminodibenzyl in the form of injection of 25 mg/5 ml or tablets of 25 mg respectively. Four of the persons hospitalized were suffering from severe endogenous depression and three were suffering from severe schizophrenia.

The following is a report of the cases:

c) Endogenous depression

Case No.	Age	Predominant Symptoms	Injection	Dosage tablets	Duration of treatment	Drive	Effect Food	Others
27 ♂	V	Inhibition		3x2 3x1	2 days 9 days	+++	++	
28 ♂	III	Inhibition		3x2 3x1	4 days 3 weeks	++	+	
29 ♂	IV	Inhibition		3x2 3x1 2x1	3 days 2 days 4 days	+++	++	Increasing excitation
30 ♂	IV	Inhibition	3x1		6 days	+++	+	Increasing excitation

+++ = remission or much improved

++ = moderately improved

+ = slight effect

c) Schizophrenia

Case No.	Age	Predominant Symptoms	Injection	Dosage tablets	Duration of treatment	Drive	Effect Mood	Others
31 ♂	III	depressive mood		3x1	7 days	+++)	+++	
32 ♂	III	depressive mood		3x1	10 days	+++	++	
33 ♂	II	depressive mood		3x2 3x1	6 days 3 weeks	++	++	

+++ = remission or much improved

++ = moderately improved

+) = excitation condition on the 6th day

C. Conclusions

Institutionalized severe endogenous depressives and severe depressive schizophrenics treated with 3,7-dichloro-5-(γ -dimethylaminopropyl)-iminodibenzyl showed little or no relief. In contrast similar severe depressives treated with 3-chloro-5-(γ -dimethylaminopropyl)-iminodibenzyl showed a satisfactory effect, which improvement was due to 3-chloro-5-(γ -dimethylaminopropyl)-iminodibenzyl. The drive of the patients as well as the mood of the patients treated with 3-chloro-5-(γ -dimethylaminopropyl)-iminodibenzyl were moderately to much improved, while there was very little or no improvement in the drive and mood of the patients treated with 3,7-dichloro-5-(γ -dimethylaminopropyl)-iminodibenzyl.

And I make these declarations sincerely.

W. Goldinger

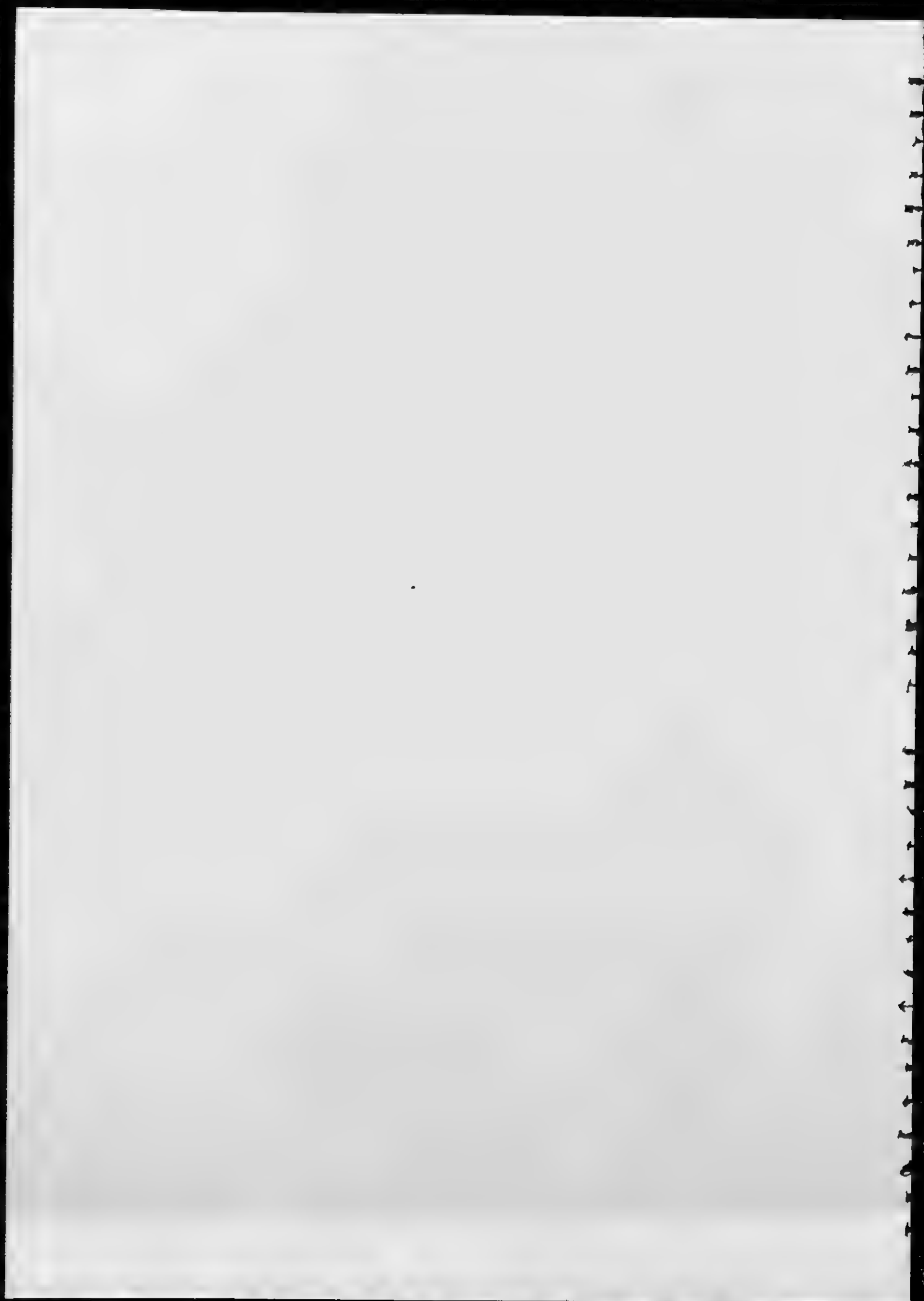
State of California
County of Los Angeles
City of Los Angeles
Consulate of the United States of America

Subscribed and sworn to before me this
day of February 1962

13th

Russell D. Fritchett

Russell D. Fritchett
Vice Consul of the
United States of America



Plaintiffs' Exhibit 1.

*Plaintiffs' Exhibit 1.***Paper No. 10—Affidavit of Dr. G. Garrone.**

BOARD OF APPEALS
MAR 7 1957
U. S. PATENT OFFICE

Schindler et al. Division 6 Case 1214/80
February 1962

Ser. No. 857,274
Filed December 4, 1959

New N-Heterocyclic Compounds

AFFIDAVIT

I, Gaston Garrone, Doctor of Medicine of the University of Turin, Italy, a citizen of Switzerland and resident of Geneva, Switzerland, being duly sworn, make the following declarations:

I am assistant medical-chief at the Psychiatric Clinic of the University of Geneva, in charge of the Psychiatric Polyclinic and the medical staff of the Medico-Pedagogic Service. I am also consultant psychiatrist at the Cantonal Hospital of Geneva as well as medical director of the Laboratory of Medical Chemistry and Endocrinology at the Psychiatric Clinic at the University of Geneva. I am professor of Clinical Psychology at the School of Social Studies in Geneva.

In 1947, I received my doctorate in medicine from the University of Turin, Italy. In the same year I obtained the Italian State Qualifying Diploma. In 1949, I received the Swiss Confederation Qualifying Diploma. I have been a recognized specialist in psychiatry for several years, being approved by the "Federation medicorum helveticorum". I have authored over thirty publications on different subjects, some of which are subsequently enumerated: (Titles translated from French)

Plaintiffs' Exhibit 1.

1. Neurotic Troubles—a case study.
(P. Schifferli and G. Garrone)
Revue médicale de la Suisse Romande LXXXVII
—58—1957
2. Elimination of steroid hormones in the urine of schizophrenics. Study of the nycturea rhythm.
(G. Garrone, P. Schifferli and G. Voldet)
Schweizerische Medizinische Wochenschrift 87,
1065, 1957
3. Practitioners treatment of the young depressed and anxious patient.
(G. Garrone)
Médecine et Hygiène—XVII, 46-47, 1959
4. Clinical study of γ -phenyl propanol carbamate, a new muscle relaxant with tranquilising activity.
(G. Garrone, P. Dick and R. Tissot)
Neuro-psychopharmacology 1, 568, 1959
5. New pharmacological therapy of the depressive state.
(G. Garrone and P. Dick)
Bulletin de l'Académie suisse des sciences médicales 15, 308, 1959
6. Treatment of the depressive state with Iproniazid.
(P. Dick and G. Garrone)
Neuro-Psychopharmacology 1, 536, 1959
7. The relationship between the involution of endocrine glands and psychiatric affections in old age.
(G. Garrone and J. Constantinidis)
Journal suisse de Médecine 89, 1211, 1959
8. Indications for a new muscle relaxant (Gamaquil) in out-patient psychiatry.
(G. Garrone, P. Tissot and P. Dick)
Journal suisse de Médecine 90, 217, 1960

Plaintiffs' Exhibit 1.

9. Preliminary study of the therapeutic action of a new mono-amine-oxidase inhibitor (RO 5-0831)
(J. J. Burgermeister, P. Dick, G. Garrone and R. Tissot)
Praxis 49, 45, 1960
10. Modifications of serum protides and lipids in the melancolique syndrome.
(G. Voldet, P. Scheidegger and G. Garrone)
L'ancéphale 48, 510, 1959
11. Mono-amino-oxidase inhibitors in the treatment of the depressive state.
(G. Garrone and P. Dick)
Psychiat. Neurol. Basel 140, 107-114, 1960
12. Therapeutic progress in psychiatry in 1960.
(P. Dick and G. Garrone)
Médecine et Hygiène XIX, 9-10, 1961

In light of Paper No. 4 issued in the matter of the above entitled patent application on the 3rd of July 1961 I have been asked by the inventors of the subject matter of the above cited application Ser. No. 857,274 to report on some clinical tests in connection with the therapeutical action of 3-chloro-5-(γ -dimethylaminopropyl)-iminodibenzyl according to said Ser. No. 857,274. Tests having been made and achieved under my direction I beg to submit an exact report about how same were carried out.

Under my supervision twenty-three ambulatory patients suffering from endogenous, reactive or/and involutional depressions were treated with 3-chloro-5-(γ -dimethylamino-propyl)-iminodibenzyl at the Psychiatric Polyclinic of the University of Geneva. The average dosage per os amounted to 50-75 mg/day. The following is a report of the cases:—

*Plaintiffs' Exhibit 1.**Case 1*

M.B. . . . 25 years old, male

Diagnosis: depression with asthenia, insomnia and anxiety

Dosage: 75 mg/day

Latency of effect: 9 days

Result: very good effect on both the depression and the asthenia.

Case 2

A.M. . . . 55 years old, male

Diagnosis: endogenous depression of the melancholic type

Dosage: 50 mg/day

Latency of effect: 4 days

Result: a very definite improvement.

Case 3

M.P. . . . 16 years old, female

Diagnosis: asthenia based on depression, attempted suicide

Dosage: 75 mg/day

Latency of effect: 9 days

Result: great lightening of depressed mood.

Case 4

R.B. . . . 81 years old, female

Diagnosis: psycho maniac depression

Dosage: 75 mg/day initially, followed by 50 mg/day

Latency of the effect: 8 days

Result: After 8 days the treatment had a noticeable effect on the depression; but the major improvement set in at the end of one month.

Plaintiffs' Exhibit 1.

Remarks: The results achieved with this older patient are particularly interesting, as well as the high tolerability for the product.

Case 5

G.B. . . . 44 years old, male

Diagnosis: depression syndrome, dromomania, attempts of suicide.

Dosage: 25 mg/day

Latency of effect: during the first week the effect was unstable, then came a period of anxiety, which was followed by a clear cut improvement.

Case 6

P.R. . . . 57 years old, male

Diagnosis: depression relapse with fear and hypochondria.

Dosage: varying between 75 and 150 mg/day

Latency of effect: first improvement on the 3rd-4th day.

Results: major improvement set in the 12th day, after the medication was cut off a relapse set in, which improved as soon as treatment was resumed, at 75 mg/day.

Case 7

J.B. . . . 40 years old, male

Diagnosis: Relapse into the melancholic state.

Dosage: 50 mg/day

Latency of effect: 6 days

Results: very marked, definite improvement.

Plaintiffs' Exhibit 1.

Remarks: the effect of this pharmaceutical was immediate and positive, psychotherapy on the other hand proved to be ineffective.

Case 8

J.B. . . 60 years old, male

Diagnosis: severe depression of the melancholic type.

Dosage: 50 mg/day, the patient could not tolerate 75 mg/day

Latency of effect: a slight improvement set in the 3rd day, which increased during the two weeks.

Result: positive

Remarks: the effect of the medicament was certain and rapid.

Case 9

J.M. . . . 28 years old, male

Diagnosis: a very pronounced depression, acute, partly endogenous, partly reactive.

Dosage: 75 mg/day

Latency of effect: 5 days

Results: very positive, a decided improvement.

Remarks: prior to this therapy all attempts at psychoanalysis were unsuccessful; this treatment greatly aided the psychotherapeutic approach.

Case 10

A.Ch. . . . 45 years old, male

Diagnosis: cyclothymia

Dosage: 50 mg/day

Latency of effect: 3 days

Results: very positive, a very definite improvement

Plaintiffs' Exhibit 1.

Remarks: the medicament had a rapid therapeutic effect at low dosage.

Case 11

B.P. . . . 48 years old, female

Diagnosis: reactive depression

Dosage: 50 mg/day

Latency of effect: 6 days

Results: a very positive effect on the depressive state

Remarks: remarkable results were attained which made it possible to treat by means of psychotherapy the persisting hysteroid tendencies.

Case 12

J.M. . . . 42 years old, female

Diagnosis: relapse into depression of a partially endogenous and partially reactive nature. All treatments were ineffective.

Dosage: 50 mg/day

Latency of effect: 4 days

Results: very positive

Remarks: a rapid and positive psychochemotherapy for a relapse into endogenous depression.

Case 13

R.L. . . . 55 years old, female

Diagnosis: relapse into depression of a partly reactive nature with serious threats of suicide.

Dosage: 50 mg/day

Latency of effect: 3 days

Results: very positive

Remarks: in this case the effectiveness of the treatment was pronounced and it set in very rapidly.

*Plaintiffs' Exhibit 1.**Case 14*

M.P. . . . 52 years old, female

Diagnosis: depression with asthenia, insomnia and anxiety.

Dosage: 75 mg/day

Latency of effect: 6 days

Results: greatly improved humor and sleep. The asthenia remained little changed.

Case 15

MB. . . . 56 years old, female

Diagnosis: reactive depression (anxiety, asthenia, hypermotility, lack of interest, dysphoria, suicide notions, insomnia, inappetence)

Dosage: 50 to 75 mg/day

Latency of effect: 5 days

Results: excellent, progressive and complete disappearance of all the troubles listed above.

Remarks: this psychochemotherapy proved to be good, effective and rapid, it did not change the conflicting situation by as much.

Case 16

Ch.Sch. . . . 46 years old, female

Diagnosis: reactive depressions which failed to respond to two hospitalizations and its treatments.

Dosage: 75 mg/day

Effect of latency: 2 days

Results: excellent and rapid

Remarks: after one month's treatment the patient suffered a slight, temporary relapse, which cleared rap-

Plaintiffs' Exhibit 1.

idly and did not recur. The effect of the medicament is evident in view of the fact that the conflicting situation has not changed.

Case 17

Y.F. . . . 39 years old, female

Diagnosis: depression of a partly reactive nature with suicide attempt.

Dosage: 50 mg/day

Latency of effect: about 3 days

Result: very good. The patient was relaxed but somewhat weary. This weariness was sometimes tainted with indifference.

Case 18

N.D. . . . 36 years old, female

Diagnosis: bouts of premenstrual depression accompanied with restlessness, nervousness, irritability, dysphoria, suicide notions and impulsive suicide attempts.

Dosage: 25 mg/day, 10 days before the period

Latency of effect: difficult to establish

Result: subjective improvement, the patient is calmer, more stable and holds herself better in check than before the treatment.

Case 19

J.F. . . . 70 years old, male

Diagnosis: endogenous depression with serious suicide attempt (a brother has committed suicide)

Dosage: 75 mg/day

Latency of effect: 3 days

Plaintiffs' Exhibit 1.

Results: disappearance of all the tenacious difficulties which comprised the symptoms of this depression that troubled the patient for years already. The result is spectacular.

Remarks: for years the patient had tried all the known makes of sleeping pills without achieving a calm and continual sleep. Since the therapy with 3-chloro-5-(γ -dimethylamino-propyl)-iminodibenzyl he sleeps without recourse to other products.

Case 20

J.A. . . . 32 years old, male

Diagnosis: a homosexual with a reactive depression

Dosage: 25 mg/day

Latency of effect: difficult to ascertain—patient left to convalesce at the beginning of the treatment.

Results: definite recovery from the symptoms which accompanied this reactive depression. The result is good, however, the reactive depression has not disappeared completely.

Remarks: although the patient is not longer in our care, we have been informed that his state has remained stable.

Case 21

J.R. . . . 40 years old, female

Diagnosis: reactive depression with nightmares and psychosomatic disorders.

Plaintiffs' Exhibit 1.

Dosage: 75 mg/day
Latency of effect: 5 to 6 days
Results: from the onset of the treatment a noticeable decrease of the depressive phenomena, revealing temporary slight depressive heaves of small consequence. The night phenomena disappeared. The result can be considered as being very good.

Case 22

M.A. . . . 47 years old, female
Diagnosis: acute depression with hysteria
Dosage: 50 mg/day
Latency of effect: 5 days
Result: greatly improved mood.

Case 23

A.L. . . . 65 years old, male
Diagnosis: involutional melancholia
Dosage: 50 mg/day
Latency of effect: 12 days
Result: greatly improved mood and the disappearance of anxiety.

Conclusion

I have found 3-chloro-5-(γ -dimethylaminopropyl)-iminodibenzyl to be an effective antidepressive. From the foregoing cases, it can be seen that twenty-three patients suffering from endogenous, reactive and/or involutional depressions on treatment with 3-chloro-5-(γ -dimethylaminopropyl)-iminodibenzyl showed a marked improvement. In other words a favourable therapeutic effect was achieved because of 3-chloro-5-(γ -dimethylaminopropyl)-iminodibenzyl. The average dose per

Plaintiffs' Exhibit 1.

day of active ingredient given was 50 to 75 mg. The period of latency between the outset of the treatment and the first effect is short, usually between 4 and 6 days, a positive response manifesting itself as early as on the 2nd day of treatment. The compound, 3-chloro-5-(γ -dimethylaminopropyl)-iminodibenzyl, is of great interest to us. Its therapeutic effect manifests itself faster than that of any other known thymolepticum. Any side effects do not differ from those which can be observed under the same conditions as to the therapeutic effect with other commercial psychotropic drugs.

CONFEDERATION OF SWITZERLAND	} S.S.
CITY AND CANTON OF GENEVA	
CONSULATE GENERAL OF THE UNITED STATES	
OF AMERICA	

Subscribed and sworn to before me,
 Harmon E. Kirby, Vice Consul of the United
 States of America in and for the consular district
 of Geneva, Switzerland, duly commissioned and
 qualified, this 16th day of February, 1962, A.D.

HARMON E. KIRBY
 Harmon E. Kirby
 Vice Consul of the
 United States of America

Service No. 6
 Tariff Item No. 45
 Fee Paid: U. S. \$2.50
 Local Cy. Equiv. S. Frs. 11

(Seal)

Plaintiffs' Exhibit 1.

Paper No. 11, Official Letter of March 21, 1962.

U. S. DEPARTMENT OF COMMERCE
PATENT OFFICE
Washington

• • • • •

In response to the letter and affidavits under
Rule 132 of March 7, 1962.

The remarks of applicants and the affidavits have been carefully considered but are not deemed to overcome the rejections as set forth in the Final Rejection.

The affidavits presented do not touch the merits of the rejection of the claimed compounds as being obvious to one skilled in the art under 35 U.S.C. 103. These affidavits and the remarks relate rather to the method of using the compounds claimed which is not in issue here.

It is additionally noted that the affidavits do not offer a comparison of the claimed compound with the compound of the prior art since there is no showing that the mono-chloro compound would have been effective against the patients to which the di-chloro compound was administered and found to be ineffective. It is consistent with the affidavit that the mono-chloro compound would also have been ineffective against these patients. In the alternative there is no showing to indicate that the di-chloro compound would not also have been effective against the patients which were shown to respond to treatment with the mono-chloro compound. The affidavits presented are therefore not deemed to provide a basis for a comparison of the compounds utilized. In this respect note also that there is no indication that the selection of the patients was on a random basis.

The rejections as set forth in the Final Rejection are deemed sound and are maintained.

The application has been returned to the Board of Appeals to await applicants' perfection of the appeal.

S. M.
T. Miller:mlb

S. MARCUS,
Acting Examiner.

Plaintiffs' Exhibit 1.

Paper No. 17—Affidavit of H. Kunz.

Walter Schindler et al. Division 6 Case 1214/80
October 1962

Serial No. 857,274
Filed December 4, 1959

New N-Heterocyclic Compounds

AFFIDAVIT

I, HEINRICH KUNZ, a citizen of the Swiss Confederation and a resident of Zurich, Switzerland, being duly sworn, depose and say:

That I am a pharmacologist of the University of Zurich, Switzerland, and that I have been active in the field of pharmacological research for 10 years; that I have read the affidavits by Heinrich Wirz filed January 3, 1962 in the United States Patent Office in patent application Serial No. 857,274 supra; that I have frequently tested chemical compounds for their spasmolytic activity, particularly by causing surviving intestine of guinea pig (according to Magnus) in a tyrode solution to contract by means of applying thereto a standard dose of acetylcholine and varying doses of substances to be tested, whereby that amount of such substances is determined which has the same lytic effect as atropine applied to the acetylcholine contracted intestine; that values above 30 are not indicative of any useful spasmolytic activity of the tested substance, while doses smaller than 15 are a satisfactory indication for useful spasmolytic activity.

I make these declarations sincerely.

Plaintiffs' Exhibit 1.

Paper No. 22—Board of Appeals Decision.

MAILED

Oct 25 1963

Appeal No. 34-57

al

U. S. PATENT OFFICE
BOARD OF APPEALS

IN THE UNITED STATES PATENT OFFICE

BEFORE THE BOARD OF APPEALS

Ex parte Walter Schindler
and Henri Dietrich .

Application for Patent filed December 4, 1959, Serial
No. 857,274. New N-Heterocyclic Compounds.

Wenderoth, Lind & Ponack for appellants.

Before Federico and Rosa, Examiners-in-Chief, and Stone,
Acting Examiner-in-Chief.

Stone, Acting Examiner-in-Chief.

This is an appeal from the final rejection of claims 1, 3, 4, 6 to 13, 16 and 17, which are all the claims remaining in the application. Subsequent to the appeal, claim 1 was cancelled. The appeal as to this claim is dismissed. Claims 3, 9, 10, 12 and 13 stand withdrawn from prosecution as they have not been acted upon as to their merits in accordance with appellants' compliance with Sec. 706.03(1)

Plaintiffs' Exhibit 1.

of the Manual of Patent Examining Procedure. Accordingly, these claims are not before us for consideration of their merits in this appeal. These claims however, will be considered with reference to the rejection based on undue multiplicity of claims. The claims before us for all purposes are claims 4, 6, 7, 8, 11, 16 and 17.

Claims 7, 8 and 16 are illustrative and read as follows:

7. 3-Ethyl-5-(a-dimethylamino-propyl)-iminostilbene.

8. 3-Chloro-5-(a-dimethylamino-propyl)-iminodibenzyl.

16. 3-chloro-5-[N¹-methyl-piperidyl (2¹)-ethyl]-iminodibenzyl.

The references relied on are:

Schindler et al	2,813,857	Nov. 19, 1957
Austrian Patent	200,578	Nov. 10, 1958
Australian Patent	215,335	June 11, 1958

The claims are directed to various species of substituted iminodibenzyl and iminostilbene compounds which are stated, on page 2 of the specification, to have certain pharmacological properties such as sedative, spasmolytic, antiemetic, etc.

The references are adequately described on pages 1 and 2 of the Examiner's Answer.

The claims stand rejected as unpatentable over the references relied on and also as unduly multiplied.

With respect to the rejection of claims 4, 6, 8 and 11 as unpatentable over Schindler et al. taken in view of the Australian patent, it is the Examiner's position that it would be obvious to one skilled in the art to modify the iminodibenzyl compounds disclosed by Schindler et al. in the manner taught by the Australian patent. The iminodibenzyl compounds disclosed by Schindler et al. are closely related to the iminodibenzyl compounds disclosed by the

Plaintiffs' Exhibit 1.

Australian patent. Schindler et al. disclose dihalo derivatives, such as 3,7-dichloro-iminodibenzyl compounds, whereas the Australian patent indicates that in iminodibenzyl compounds very similar to those disclosed by Schindler et al. that dihalo derivatives are equivalent to monohalo, dialkyl and monoalkyl derivatives of iminodibenzyl. In the Australian patent the iminodibenzyl compounds are limited to a piperazino "tail" whereas the Schindler et al. reference discloses the broad range of equivalency between amino containing "tail" moieties. Appellants urge that Schindler et al. is limited to dihalo derivatives whereas the monohalo and monoalkyl derivatives are instantly claimed and the affidavits of record indicate the nonequivalency of the mono- and di- derivatives.

Appellants' arguments with respect to the rejection of claims 4, 6, 8 and 11 as being unpatentable over Schindler et al. taken in view of the Australian patent are not persuasive. The iminodibenzyl compounds found in Schindler et al. are not only closely related structurally to the iminodibenzyl compounds found in the Australian patent, but the pharmacological properties are the same as is evident in comparing col. 2 in the Australian patent with column 1, lines 38 to 41 in Schindler et al. The affidavits which appellants urge disclose the nonequivalency between the mono- and the dichloro, etc. derivatives of iminodibenzyl compounds are not controlling since the affidavits are either not directed to the species of claims 4, 6 and 11 or, as with claim 8, the affidavits show a difference in degree rather than a difference in kind. Thus, insofar as claim 8 is concerned, the instant case is unlike the situations presented in *In re Papesch*, 50 CCPA —, 315 F. (2d) 381, 137 USPQ 43; *In re Lambooy*, 49 CCPA 985, 780 O. G. 703, 1962 C. D. 224, 300 F. (2d) 950, 133 USPQ 270; or *In re Petering et al.*, 49 CCPA 993, 780 O. G. 710,

Plaintiffs' Exhibit 1.

1962 C. D. 232, 301 F. (2d) 676, 133 USPQ 275, in which the utility of the claimed compound differed radically from that of the reference compounds. The utility for the compound of claim 8, which compound is deemed obvious from the references, is the same as the utility of the reference compounds and the difference in pharmacological properties is one of degree rather than in kind. It is believed obvious for one skilled in the art to modify the compounds disclosed by Schindler et al. in the manner suggested by the Australian patent and it would be expected that such compounds would have no more than the expected pharmacological properties. The Poldinger affidavit, paper No. 10, and the Wirz affidavit, paper No. 6, which compare as to pharmacological properties, the compound of claim 8 with its dichloro analog as disclosed in Example 2 of Schindler et al. are not persuasive since said affidavits indicate that the Schindler et al. compound has the same utility as the claimed compound and differs therefrom merely in degree. The rejection of claims 4, 6, 8 and 11 on Schindler et al. in view of the Australian patent is therefore sustained.

• • • • •

Plaintiffs' Exhibit 2.

Paper No. 23—Notice of Civil Action.

**U. S. DEPARTMENT OF COMMERCE
PATENT OFFICE
Washington**

**Re: Application of
Schindler et al
S. N. 857,274
Filed December 4, 1959
For: New N-Heterocyclic
Compounds**

NOTICE OF CIVIL ACTION UNDER 35 U. S. C. 145

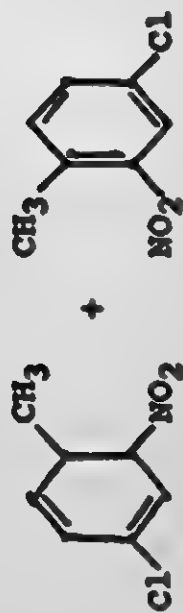
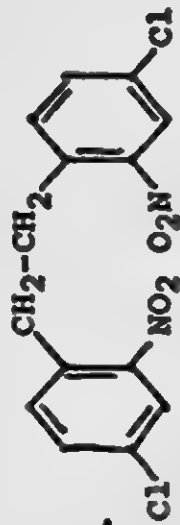
A civil action No. 3068-63, under 35 U. S. C. 145, entitled Walter Schindler and Henri Dietrich v. Commissioner of Patents, involving this application, was filed in the United States District Court for the District of Columbia, on December 24, 1963.

**C. W. MOORE,
Solicitor.**

Plaintiffs' Exhibit 2.

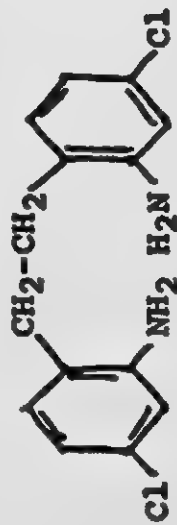
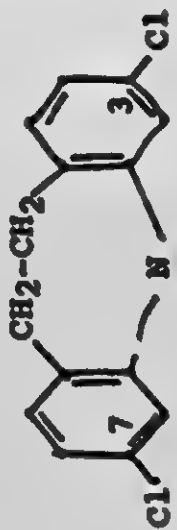
(See opposite )

AND 5-(3-DIMETHYLAMINOPROPYL)-3,7-DICHLORO-IMINO-

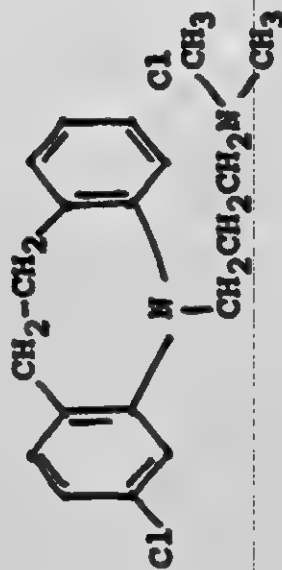
DIBENZYL(Compound of Example 2
of U.S. 2,813,857)"Coupling"

Key Intermediate I.

Reduction

Cyclization

Key-Intermediate II



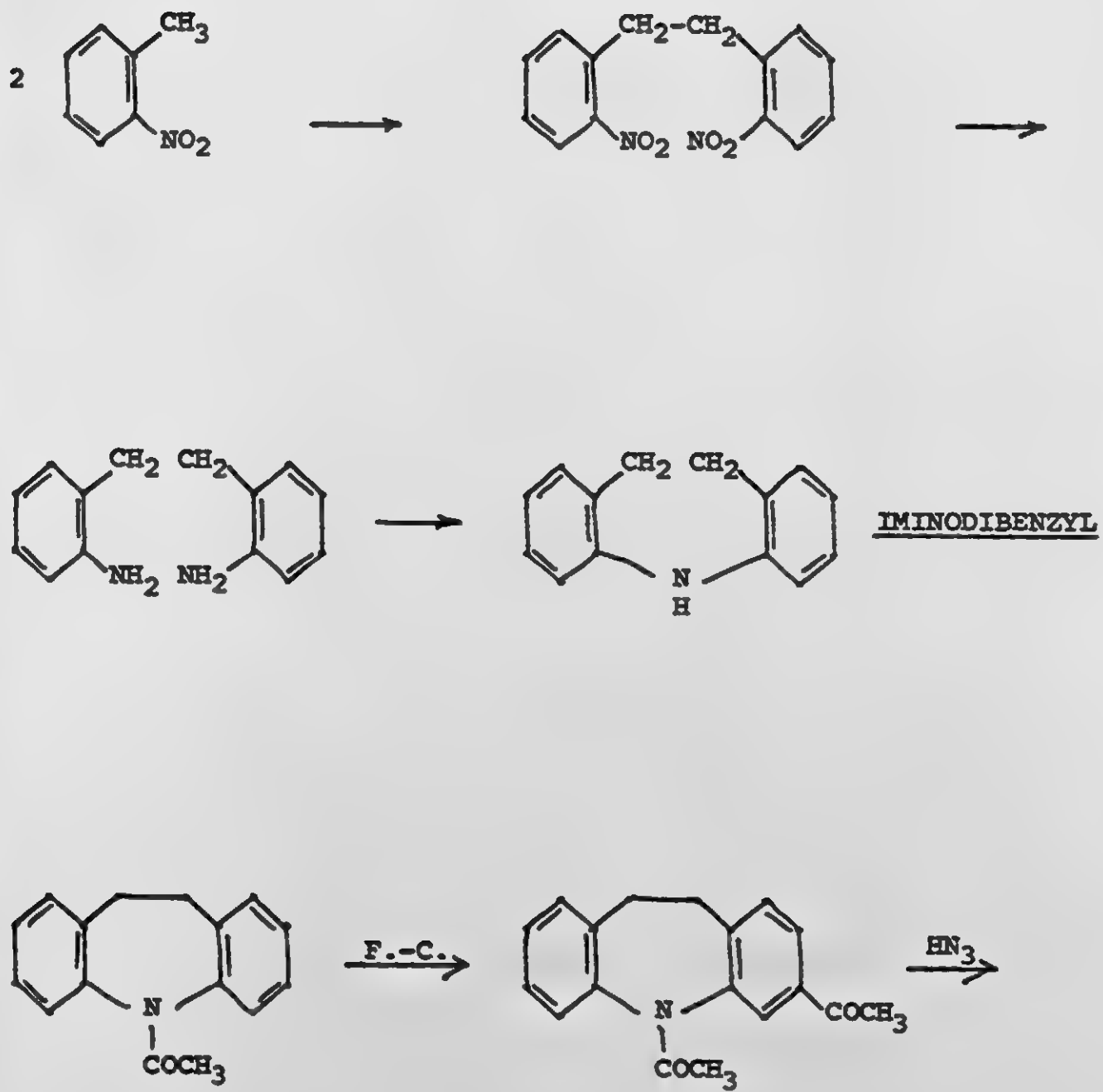
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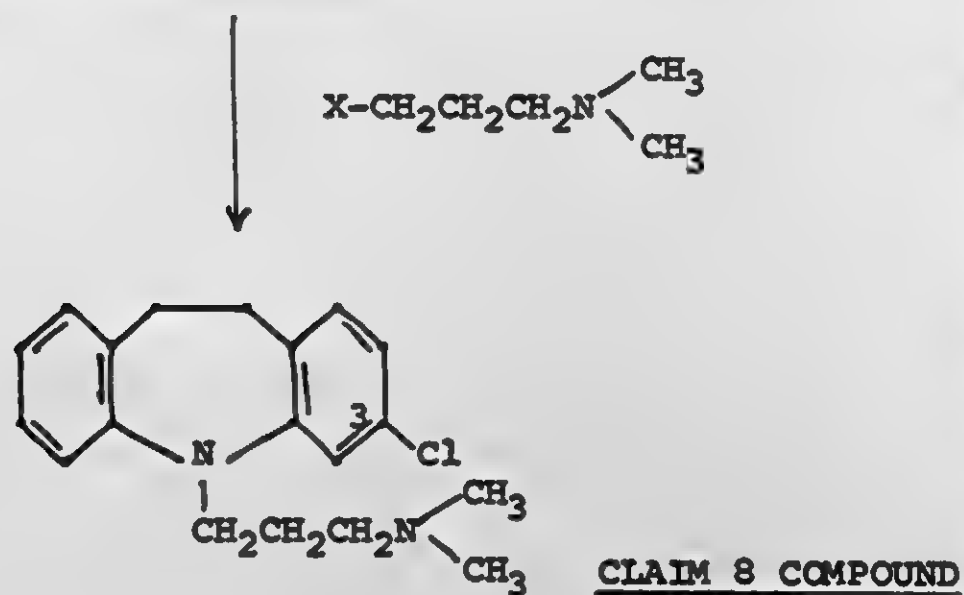
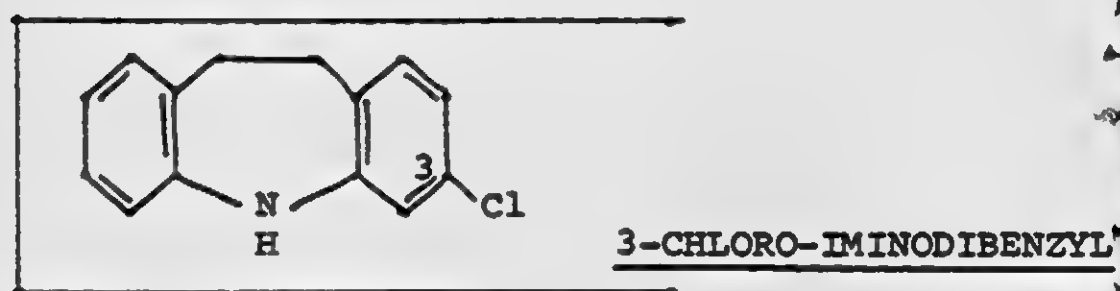
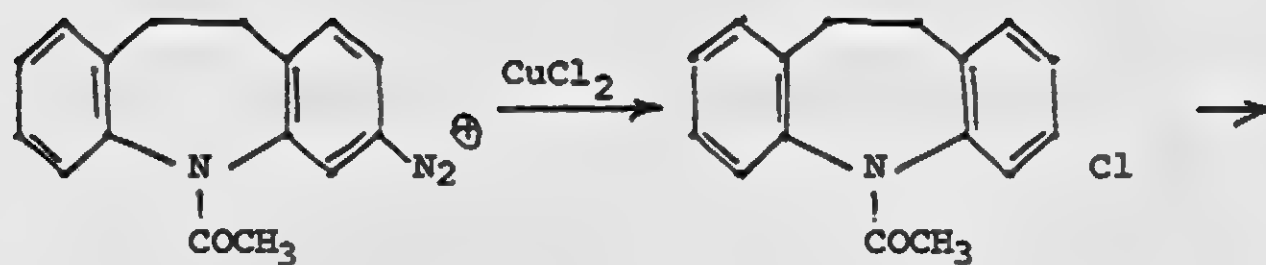
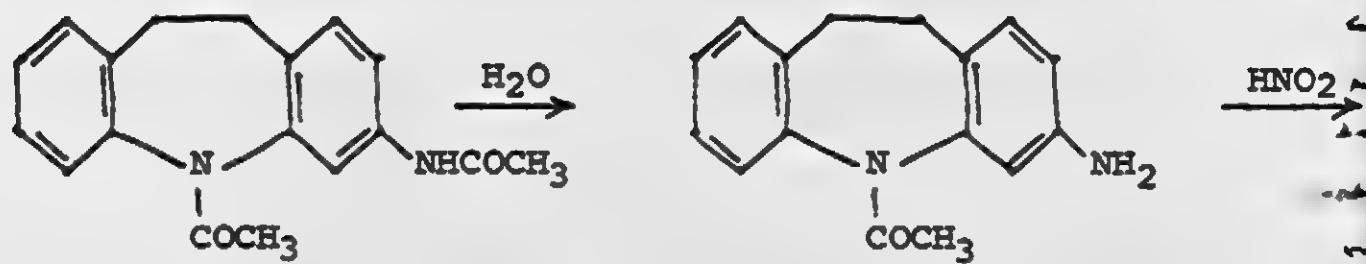
Plaintiffs' Exhibit 3.

(See opposite )

CHART 3.

SYNTHESIS OF 3-CHLORO-IMINODIBENZYL





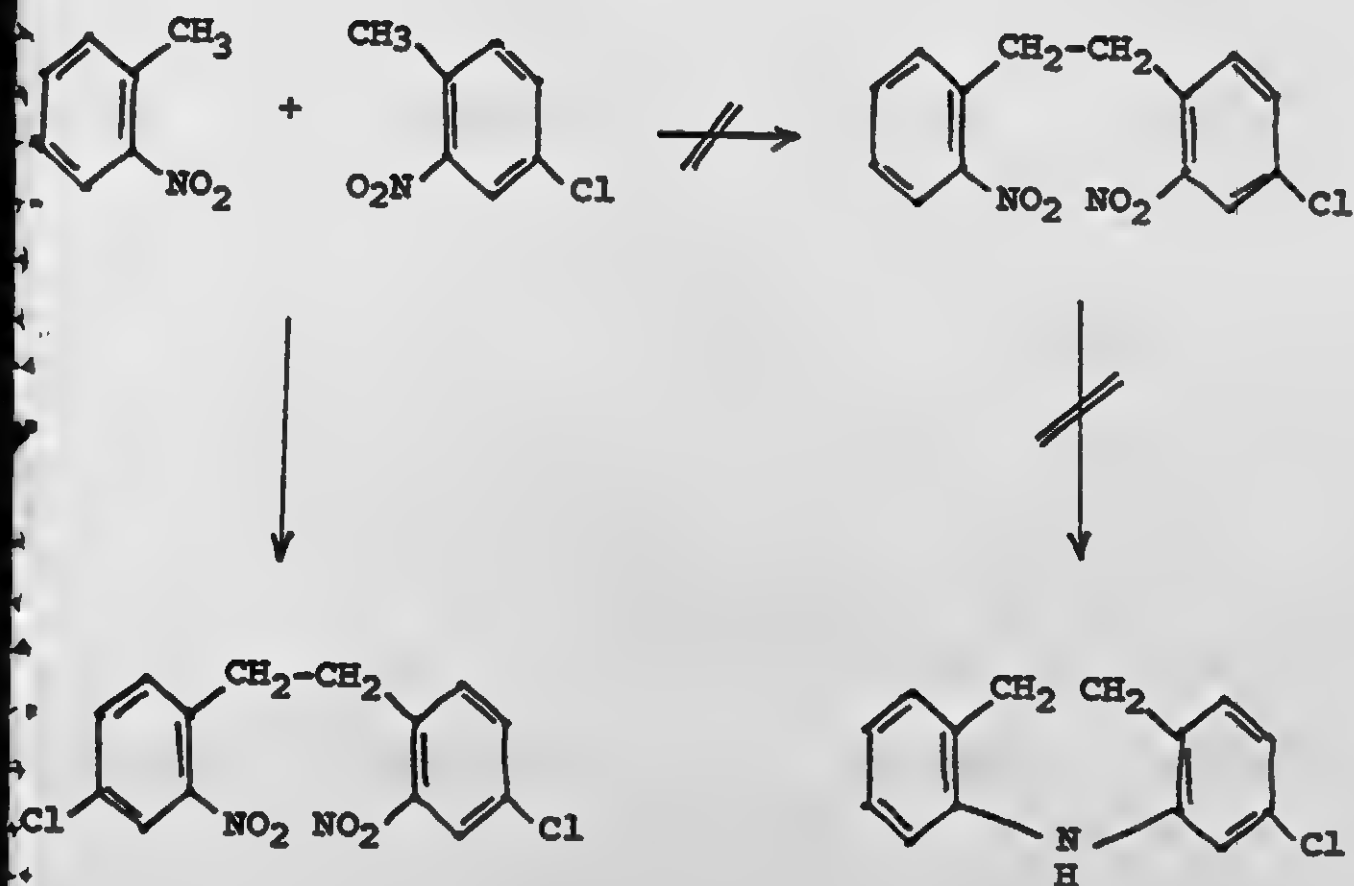
11 STEPS

Plaintiffs' Exhibit 4.

(See opposite )

CHART 2.

ATTEMPTED SYNTHESIS OF 3-CHLORO-IMINODIBENZYL



Plaintiffs' Exhibit 5.

(See opposite **119**)

SELECTIVE TOXICITY

with special reference to
CHEMOTHERAPY

ADRIEN ALBERT

D.SC. (LOND.), PH.D. MEDICINE (LOND.), F.R.I.C.

PROFESSOR OF MEDICAL CHEMISTRY IN THE
AUSTRALIAN NATIONAL UNIVERSITY

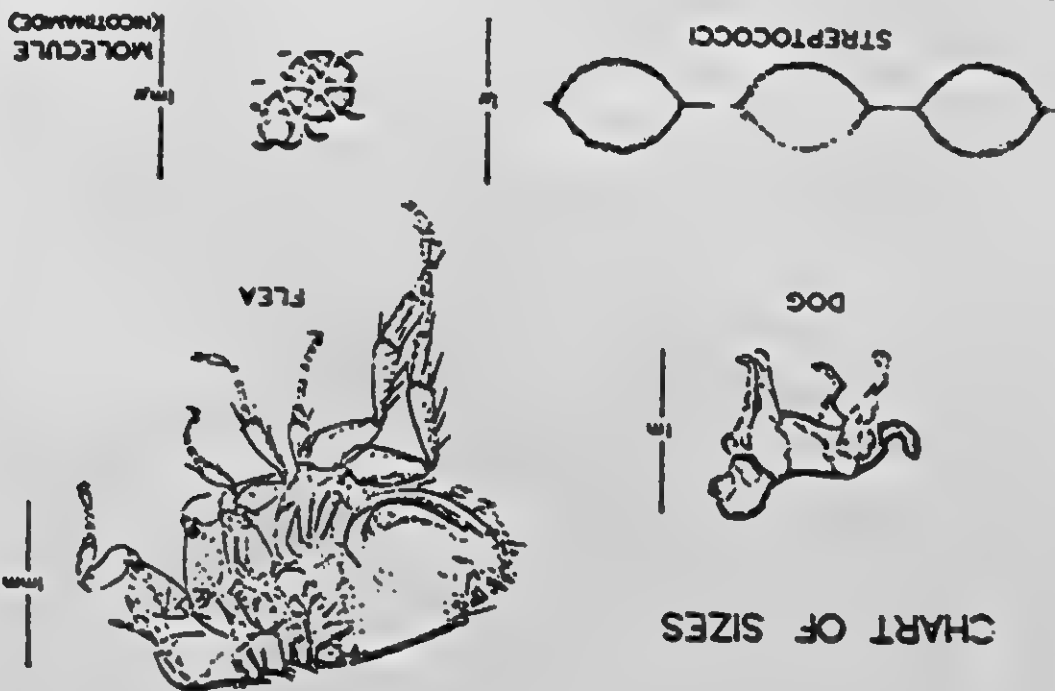
HONORARY LECTURER IN THE DEPARTMENT OF BIOCHEMISTRY,
UNIVERSITY COLLEGE, LONDON

WITH 5 PLATES AND 31 DIAGRAMS

LONDON: METHUEN & CO. LTD.

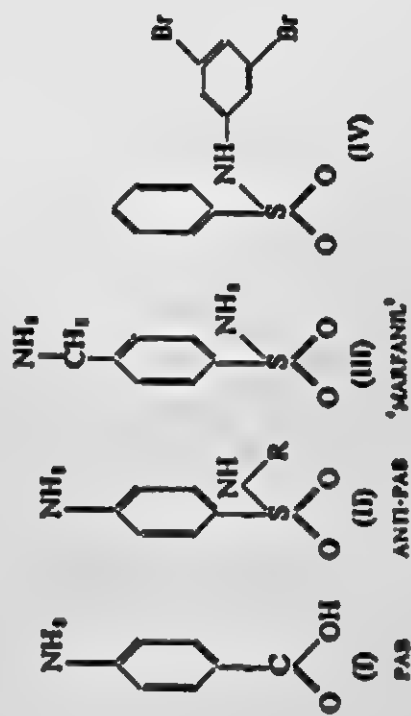
NEW YORK: JOHN WILEY & SONS, INC.

This chart is to help one remember the relative sizes of Molecules, Microbes, Insects and Mammals. In each case a fairly small example has been chosen (e.g. Dog and not Whale). Each object is drawn with a magnification 1000 times greater than the object preceding it.



Compared with the heteroaromatic kationic antibacterials, described in Chapter IV, its action is feeble.

The third class of sulphonamides, represented by formula (IV), lacks the *p*-amino group typical of the first class, but has as its *R*-group a nucleus with strongly electron-attracting substituents. Members of this class are not antagonized by *p*-aminobenzoic acid (Goetchius and

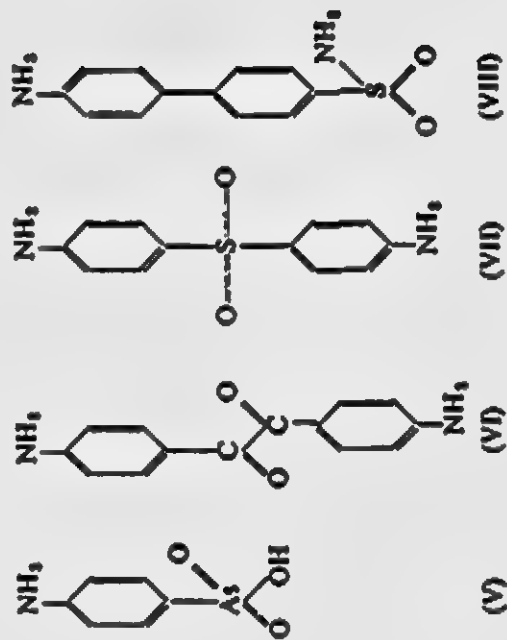


Lawrence, 1945; Schmidt and Sesler, 1946). No pK_a values for them have been recorded, but they appear to be well-ionized acids and may turn out to be functioning as simple anionic antibacterials, like dodecane sulphonic acid, in which case they will be antagonized by hydroxyl ions (cf. Chapter IV). No member of this class has been found sufficiently active to be given a place in clinical medicine. If an amino-group is inserted in the same position as in sulphanilamide, substances are obtained whose action is partly antagonized by *p*-aminobenzoic acid.

Obviously a special name is required for those sulphonamides which compete with *p*-aminobenzoic acid (PAB). To coin new names unnecessarily is undesirable, but here the need is acute. I suggest that these substances be called

anti-pabs. This name is not musical to the ear, but it is self-explanatory. Let us use it until someone suggests something better.

All *anti-pabs*, be it noted, are not sulphonamides and some of them do not contain any sulphur at all. All that is needed is that the molecules of these metaboliteanalogues should have a sufficient (but not too great) degree of



resemblance to the molecule of *p*-aminobenzoic acid. The insertion of a methyl-group into the 2- or 3-positions of PAB gives intermediate types which have neither *pab* nor *anti-pab* activity. However, the insertion of a chlorine atom into either the 2- or 3-positions of PAB makes an active *anti-pab* (Wyss, Rubin and Strandskov, 1943).

p-Aminobenzenearsonic acid ('atoxyl' V) is another *anti-pab*. In general, arsonic acids are not antibacterial (cf. Albert, Falk and Rubbo, 1944), but this substance (V) forms an exception. The reason is that it is the only arsenical which resembles *p*-aminobenzoic acid sufficiently well to be able to compete with it (Hirsch, 1942). Another

APPENDIX I

CONNECTION BETWEEN IONIZATION AND ANTIBACTERIAL ACTIVITY IN THE ACRIDINE SERIES.
HIGHEST DILUTIONS COMPLETELY PREVENTING VISIBLE GROWTH IN 48 HOURS AT 37° C.

Medium: Broth containing 10 per cent of serum; pH 7.2-7.4

Key to dilutions:

0 signifies growth at 1 in 5,000

1 signifies inhibition at 1 in 5,000

2 " " " 10,000

3 signifies inhibition at 1 in 20,000

4 " " " 40,000

5 " " " 80,000

6 " " " 160,000

7 signifies inhibition at 1 in 320,000

8 " " " 640,000

9 " " " 1,280,000

10 " " " 2,500,000

No.	Substance	Organisms					Bacteriostatic Index (sum total of code number of inhibitory dilutions)	pK _a in water at 37°	Per cent ionized (cation) at 37° C. and pH 7.3
		Cl. welchii	Strept. pyogenes	Staph. aureus	B. coli	Proteus			
1	Acridine	3	1	1	0	1	6	5.3	1.0
2	1-Methylacridine	2	0	0	0	0	2	5.2	0.9
3	3-Methylacridine	0	0	0	0	0	0	5.9	4.0
4	5-Methylacridine	3	0	0	0	0	3	6.0	5.0
5	1:3:4:6:7:9-Hexamethylacridine	0	0	0	0	0	0	4.3	>0.1
6	1-Methoxyacridine	3	0	0	0	0	3	4.6	0.2
7	3-Methoxyacridine	3	2	1	0	0	6	4.7	0.3
8	2:8-Dimethoxyacridine	5	4	0	0	0	9	6.1	6.0
9	1-Acetamidoacridine	2	1	0	0	0	3	2.9	>0.1
10	2-Acetamidoacridine	2	2	0	0	0	4	5.5	1.6
11	3-Acetamidoacridine	4	2	1	1	1	9	4.6	0.2
12	4-Acetamidoacridine	0	0	0	0	0	0	4.3	0.1
13	5-Acetamidoacridine	0	0	0	0	0	0	4.2	>0.1
14	1-Hydroxyacridine	3	4	3	0	0	12	4.6	0.2
15	2-Hydroxyacridine	3	2	1	0	0	6	5.3	1.0
16	3-Hydroxyacridine	0	0	0	0	0	0	4.6	0.2
17	4-Hydroxyacridine	0	0	0	0	0	0	4.9	0.1
18	5-Hydroxyacridine (acridone)	0	0	0	0	0	0	>1	>0.1
19	1-Aminoacridine	2	1	1	0	0	4	4.2	>1
20	2-Aminoacridine	6	5	3	4	3	21	7.7	73
21	3-Aminoacridine	3	2	1	0	0	8	5.6	2
22	4-Aminoacridine	5	2	1	1	0	9	5.7	2
23	5-Aminoacridine (Acramine, B.P.)	7	6	4	4	4	25	9.6	100
24	3-Aminoacridan	2	2	1	0	0	5	5.1	0.6
25	1:5-Diaminoacridine	5	5	4	4	4	22	9.0	98
26	1:9-Diaminoacridine	0	0	0	0	0	0	3.8	>1
27	2:5-Diaminoacridine	7	6	2	2	0	17	11.1	100
28	2:6-Diaminoacridine	7	7	4	4	4	26	9.0	98
29	2:7-Diaminoacridine	7	6	4	5	4	26	7.8	76
30	2:8-Diaminoacridine (Proflavine, B.P.)	7	6	4	3	2	22	9.3	99
31	2:9-Diaminoacridine	4	3	0	2	0	9	7.0	33
32	3:5-Diaminoacridine	7	6	2	2	1	18	10.0	100
33	3:7-Diaminoacridine	5	3	1	0	0	9	5.8	3
34	4:5-Diaminoacridine	5	5	3	3	2	18	10.7	100
35	3-Amino-5-methylacridine	5	3	2	0	0	10	5.8	3
36	5-Amino-1-methylacridine	7	7	5	4	4	27	9.8	100
37	5-Amino-2-methylacridine	6	6	4	3	2	21	9.8	100
38	5-Amino-3-methylacridine	7	6	4	4	2	23	9.6	100
39	5-Amino-4-methylacridine	6	7	4	4	4	25	9.6	100
40	5-Amino-1:3-dimethylacridine	8	7	5	3	1	24	10.3	100

APPENDIX 1—contd.

202

No.	Substance	Organisms					Bacteriostatic index (sum total of code numbers of inhibitory dilutions)	pK _a in water at 37°	Per cent ionized (kation) at 37° C. and pH 7.3
		Cl. welchii	Strept. pyogenes	Staph. aureus	B. coli	Proteus			
41	5-Amino-1:9-dimethyl-acridine	8	7	5	4	3	27	9.1	98
42	5-Amino-1-ethylacridine	7	6	4	3	2	22	10.0	100
43	2:8-Diamino-1:9-dimethyl-acridine	9	8	6	4	3	30	8.8	97
44	2:8-Diamino-3:7-dimethyl-acridine	8	6	4	3	0	21	9.8	100
45	2:8-Diamino-4:6-dimethyl-acridine	8	8	2	4	0	22	10.2	100
46	2-Amino-5-chloroacridine	1	0	0	0	0	1	6.4	11
47	2-Amino-7-chloroacridine	5	4	3	1	0	13	6.7	20
48	2-Amino-8-chloroacridine	4	4	3	2	0	13	7.0	33
49	3-Amino-8-chloroacridine	0	0	0	0	0	0	4.1	>1
50	5-Amino-1-chloroacridine	6	5	4	3	2	20	8.0	83
51	5-Amino-2-chloroacridine	7	6	5	5	3	26	8.7	96
52	5-Amino-3-chloroacridine	7	6	5	4	4	26	8.5	94
53	5-Amino-4-chloroacridine	6	6	4	4	2	22	8.1	86
54	2:8-Diamino-3:7-dichloroacridine	8	6	4	5	0	23	8.0	83

SELECTIVE TOXICITY

55	5-Amino-1-methoxyacridine	7	6	4	3	2	22	9.7	100
56	5-Amino-2-methoxyacridine	7	6	5	4	3	25	9.9	100
57	5-Amino-3-methoxyacridine	7	7	5	4	2	25	9.4	99
58	5-Amino-4-methoxyacridine	7	6	4	3	2	22	10.0	100
59	2:5-Diamino-7-ethoxyacridine ("rivanol")	6	7	4	3	0	20	11.2	100
60	5-Amino-2-chloro-7-methoxyacridine	8	6	5	2	0	21	8.4	93
61	5-Amino-1-hydroxyacridine	5	5	3	3	3	19	Z	24
62	5-Amino-2-hydroxyacridine	2	4	0	0	0	6	Z	9
63	5-Amino-3-hydroxyacridine	4	6	2	0	0	12	Z	56
64	5-Amino-4-hydroxyacridine	3	3	1	0	0	7	Z	2
65	5-Amino-1-nitroacridine	6	7	4	4	3	24	7.6	67
66	5-Amino-2-nitroacridine	6	10	6	5	3	30	7.6	67
67	5-Amino-3-nitroacridine	7	6	5	4	2	24	7.7	72
68	5-Amino-4-nitroacridine	7	8	6	4	2	27	7.4	56
69	5-Amino-2-nitro-7-ethoxyacridine	7	8	4	0	0	19	7.4	56
70	5-Amino-1-phenylacridine	5	5	3	2	0	15	9.0	98
71	5-Amino-3-phenylacridine	8	7	6	3	0	24	9.5	99
72	2-Amino-5-p-aminophenylacridine	6	4	3	1	0	14	8.0	83
73	2:8-Diamino-3:7-dimethyl-5-phenylacridine	5	5	5	1	0	16	9.4	99
74	5-Amino-3-cyanoacridine	7	5	4	4	3	23	7.8	76
75	5-Methylaminoacridine	7	6	4	2	3	22	9.9	100
76	2-Dimethylaminoacridine	5	5	3	2	0	15	8.1	86

APPENDICES

203

APPENDIX I—contd.

204

No.	Substance	Organisms					Bacteriostatic index (sum total of code numbers of inhibitory dilutions)	pK _a in water at 37°	Per cent ionized (calculated at 37°C. and pH 7.3)
		Cl. welchii	Strept. pyogenes	Staph. aureus	B. coli	Proteus			
77	2-Dimethylamino-7-amino-acridine	6	5	3	1	0	15	8.3	90
78	2:8-bis-Dimethylamino-acridine	5	6	4	2	0	17	10.1	100
79	5-(β-Hydroxyethyl)-amino-acridine	5	5	2	2	1	15	9.1	98
80	10-Methylacridinium hydroxide	0	0	0	0	0	0	(unstable)	?
81	2-Amino-10-methylacridinium hydroxide	6	7	1	5	0	19	12	100
82	3-Amino-10-methylacridinium hydroxide	1	2	0	0	0	3	(unstable)	?
83	4-Amino-10-methylacridinium hydroxide	3	3	2	0	0	8	(unstable)	?
84	5-Amino-10-methylacridinium hydroxide	5	6	4	4	3	23	10.7	100
85	3-Amino-5:10-dimethylacridinium hydroxide	5	5	3	2	0	15	9.4	100
86	2:8-Diamino-10-methylacridinium hydroxide	7	8	3	3	1	22	>12	100

SELECTIVE TOXICITY

87	β-Amino-5-ethylacridine	6	6	2	3	2	19	8.9	98
88	p-Amino-5-styrylacridine	0	0	0	0	0	0	5.5	2
89	Acridine-3-sulphonic acid	0	0	0	0	0	0	Z*	>1
90	Acridine-1-carboxylic acid							Z	>1
91	Acridine-3-carboxylic acid							Z	>1
92	Acridine-5-carboxylic acid							Z	>1
93	Methyl ester of last named	0	0	0	0	0	0	3.5	>1
94	2-Aminoacridine-7-sulphonic acid	1	0	0	0	0	1	Z	>1
95	2-Aminoacridine-7-sulphonamide	4	2	0	2	0	8	6.9	29
96	2-Aminoacridine-7-carboxylic acid	0	0	0	0	0	0	Z	>1
97	Methyl ester of last named	1	0	0	0	0	1	6.8	24
98	5-Aminoacridine-1-carboxylic acid	0	0	0	0	0	0	Z	>1
99	5-Aminoacridine-3-carboxylic acid	0	0	0	0	0	0	Z	>1
100	Methyl ester of last named	7	6	5	2	0	20	8.3	98
101	Amide of No. 99	3	5	2	3	2	15	8.5	96

APPENDICES

From Albert, Rubbo, Goldacre, Davey and Stone (1945); Albert and Goldacre (1948). Many pK_a values are revised, having been determined directly in water for the first time.

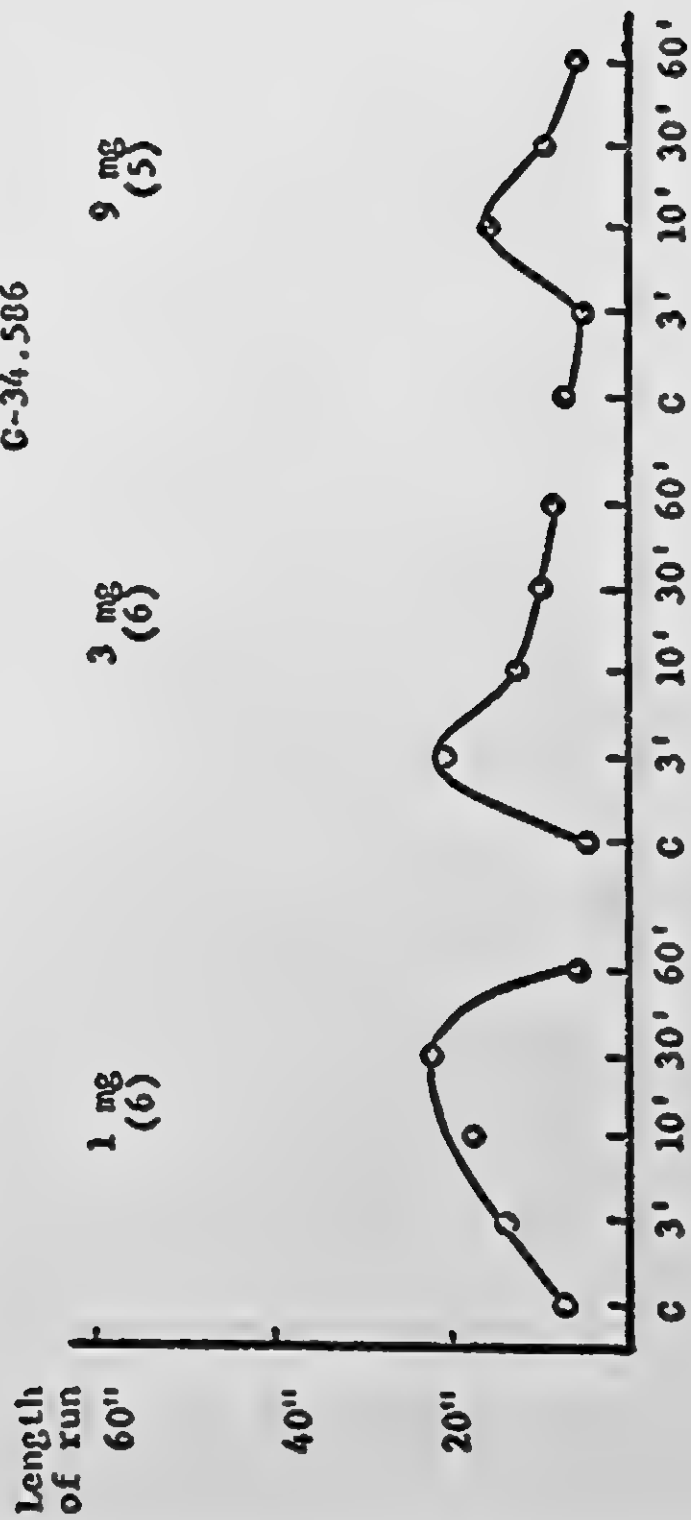
* Z—Zwitterion (see Albert and Goldacre, 1947).

205

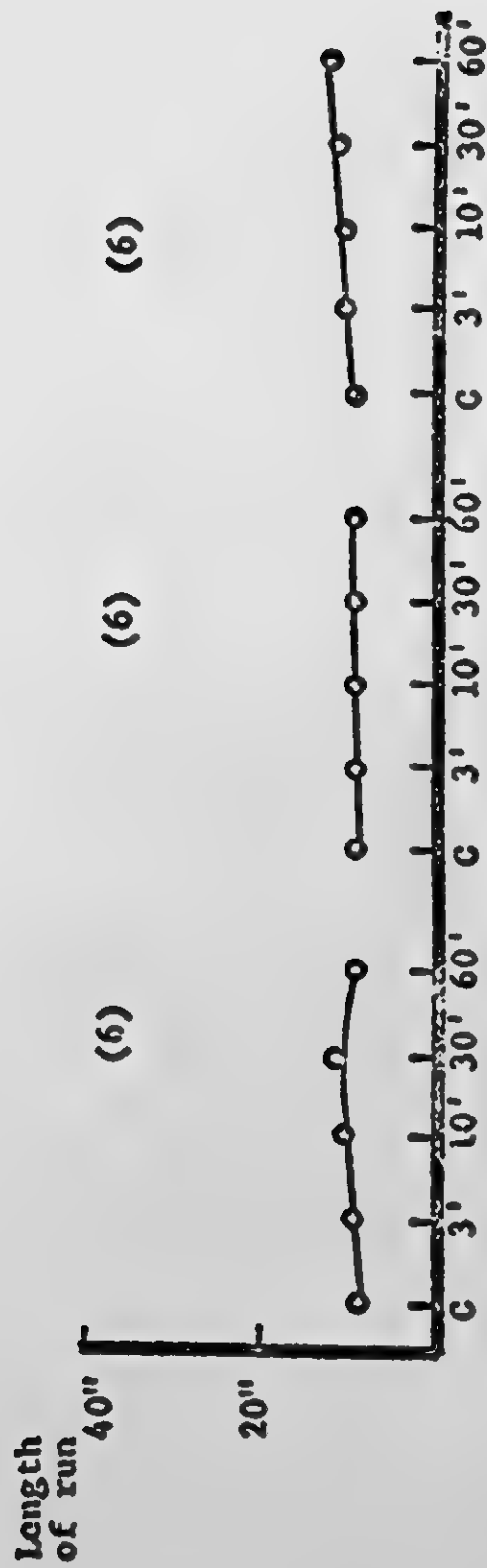
Plaintiffs' Exhibit 6.

(See opposite )

C-34.586



G-28.364*



Plaintiffs' Exhibit 7.

(See opposite )

**ANTAGONISM TO RESERPINE INDUCED DEPRESSION
BY IMIPRAMINE, RELATED PSYCHOACTIVE DRUGS,
AND SOME AUTONOMIC AGENTS**

Ernest B. Sigg, Iaszlo Gyermek* and Ronald T. Hill

The Department of Pharmacology

**Geigy Research, Division of Geigy Chemical Corp.,
Ardsley, New York (U. S. A.)**

***Present Address: Syntex Laboratories, Palo Alto, California**

In the search for laboratory procedures to uncover potential antidepressant agents, two principal approaches have been used: the enhancement of central adrenergic activity (Carlton and Didamo, 1961; Stein and Seifter, 1961; Hill *et al.*, 1961; Maxwell and Palmer, 1961), and the antagonism against experimentally induced CNS depression (Domenjoz and Theobald, 1959; Costa *et al.*, 1960; Sulser *et al.*, 1962; Askew, 1963). However, it was found that amphetamine induced excitation is not only enhanced by imipramine and amitriptyline, but also by atropine (Carlton, 1960) and several antihistaminic agents (Stein, 1962). Therefore, the question arose if potentiation of central adrenergic effects induced by amphetamine or similar agents and antagonism to reserpine and tetra-benzazine depression are related to some autonomic properties (e.g., anticholinergic, antihistaminergic and antihydroxytryptaminergic activity) inherent in the non-MAO inhibitor type of antidepressants. In order to elucidate this problem, a simple semi-quantitative procedure in mice was developed by one of us (L.G.). Imipramine and related derivatives, phenothiazines and several autonomic agents, were tested as potential reserpine antagonists. The findings are reported and discussed in this presentation.

Methods:

Swiss Albino mice of both sexes, weighing 20 - 25 grams, and fasted for 16 hours, were injected with 10 mg/kg of reserpine intraperitoneally (i.p.). Potential reserpine antagonists were injected intravenously in doses of 0.3, 1, 3, and 9 mg/kg, 90 - 120 minutes following reserpine administration. Controls received a saline injection. The animals were placed at the end of a straight narrow plastic runway 193 centimeters long. A standard pinch with a calibrated forceps was applied to the tail as external stimulus to which the mice responded with moving forward. The pinching was repeated four times more and the total distance covered by the animals was measured. The mice were tested 3, 10, 30 and 60 minutes after the injection of the test compounds. The distances run by each mouse at the four time intervals were added and averaged. The scores of all

mice in a test group were averaged and statistically compared to controls by applying Student's T-test with one-sided probabilities.

Results:

The average distance run at the four time intervals (3, 10, 30 and 60 minutes) after i.v. injection of 0.2 ml of saline, was 25 cm. (control score) in the reserpinized mouse.

Table I illustrates the changes from the control score after injection of various agents. The clinically established antidepressant agents, amitriptyline, imipramine, and desmethylinipramine (DMI), possessed reserpine antagonistic properties, DMI being the most potent antagonist (Fig. 1). The desmethyl analogs of G 38116 and G 34586, were also more potent than the corresponding tertiary amines. An increase in dose was not always followed by enhancement of reserpine antagonism. Thus, 8-HO-imipramine, G 38188 and G 34586, in increasing doses, diminished the antagonism to reserpine. Of particular interest was the finding that promazine exhibited marked antagonism to reserpine, whereas chlorpromazine exerted such an effect only after administration of the largest dose (9 mg/kg i.v.). Since the reserpine antagonism of these compounds could possibly be due to their known 5-HT blocking, antihistaminergic and anticholinergic activity, some tests with representative autonomic agents of this type were performed.

From Table II it can be inferred that, in contrast to centrally active LSD 25, peripheral 5-HT antagonists (Bromo-LSD, UML-491) did not antagonize the reserpine-induced depression of locomotor activity. Cyproheptadine, which possesses both 5-HT blocking and antihistaminergic properties, was a weak reserpine antagonist, whereas diphenhydramine and thenyldiamine, both antihistaminergic agents, were considerably more potent. Atropine, however, failed to antagonize the depressant effect of reserpine.

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Discussion:

Observation of an antagonistic action to reserpine has been utilized as a test to determine the potential antidepressant effect of centrally active agents. Pretreatment with MAO inhibitors prevents the sedative action of reserpine (Brodie et al., 1956). Imipramine antagonizes certain effects of reserpine, such as locomotor activity, ptosis, diarrhea (Domenjoz and Theobald, 1959; Costa et al. 1960) and prolongation of hexobarbital sleeping time (Sulser et al. 1960). The sedative effect of tetrabenazine, a synthetic reserpine derivative, is also antagonized by imipramine, DMI (Sulser et al., 1962) and amitriptyline (Vernier et al. 1962). However, it is recognized that dose levels, injection time schedules, and animal species are among critical factors eliciting an antagonistic response to the sedative effect of reserpine. Furthermore, imipramine antagonizes neither the reserpine induced catatonia in mice (Zetler, 1960) nor spontaneous locomotor activity as measured in a photo-electric cage (Unpublished Observations). It is therefore of interest that the reduction by reserpine of induced locomotor activity in mice can readily be counteracted by imipramine, DMI and amitriptyline. Moreover, a quantitative evaluation can be made when our procedure is used. Thus, DMI, an active metabolite of imipramine, is more potent as a reserpine antagonist than imipramine, a finding which corroborates the observation of Sulser et al. (1962). Promazine and, to a lesser extent, chlorpromazine, also counteract reserpine sedation. Imipramine and amitriptyline, like phenothiazines, possess serotonin blocking, antihistaminergic properties. Since any of these properties may account for the reserpine antagonistic effect, it is interesting that diphenhydramine and thenyldiamine diminish reserpine sedation whereas atropine does not. Since LSD 25 is itself a stimulant when given in high doses, its antagonistic effect against reserpine cannot

necessarily be related to its antiserotonin properties. Other frank CNS stimulants, such as methylphenidate and amphetamine, also counteract reserpine depression (Plummer et al., 1957). Cyproheptadine, which is both serotonin blocking and antihistaminergic, is a weak reserpine antagonist in this test. These findings are particularly noteworthy in the light of Stein's finding that not only amitriptyline, imipramine, and small doses of chlorpromazine, but also diphenhydramine, promethazine and other antihistaminic agents, potentiate the central action of amphetamine (Stein, 1962). In contrast, ataractic doses of chlorpromazine antagonize the amphetamine effect. These observations are consistent with the opposing psychopharmacological actions of imipramine and chlorpromazine. Stein refers to the observation that allergic (histamine-related) phenomena are often noted in cases of depression.

Our results are further corroborated by Askew (1963) who studied the reversal of reserpine induced lowering of body temperature in mice by a variety of centrally acting agents. He demonstrated that not only imipramine, DMI and amitriptyline antagonized reserpine induced hypothermia, but also, though to a lesser extent, chlorpromazine and phenergan, while atropine is not active in this respect. On the basis of these findings it may be speculated that reserpine antagonism induced by phenothiazines and iminodibenzyls is due to the central antihistaminic effect of these agents. It cannot be ascertained at present whether these central autonomic properties bear a relationship to the clinical effectiveness of these agents as antidepressants.

Summary:

A method for semiquantitative evaluation of potential reserpine antagonists in mice has been described. Desmethylinipramine is the most potent reserpine antagonist among several imipramine derivatives

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tested. However, promazine and antihistaminic agents also antagonize the effects of reserpine, whereas atropine and serotonin antagonists fail to do so. It is speculated that the antihistaminergic properties of these compounds are, at least partly, involved in the mechanism of reserpine antagonism.

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TABLE I

Average Change in Running Distance per Mous: Centimeter

Doses in mg/kg 1.v.

Structure	R ₁	R ₂	R ₃	Designation	0.3	1	3	9
	CH ₃	H	H	Imipramine	-	8 (8)*	9 (8)**	21 (8)**
	H	H	H	DOX	28 (21)**	31 (83)**	64 (26)**	-
	CH ₃	H	OH	0 33 679	4 (4)	58 (6)**	39 (12)**	35 (6)**
	CH ₃	Cl	H	0 34 586	-	14 (5)**	8 (6)*	-11 (5)
	H	Cl	H	OP 38 025	-	23 (12)**	21 (11)**	3 (12)**
	CH ₃	H	H	0 31 406	3 (6)	19 (6)**	27 (6)**	6 (6)**
	H	H	H	0 35 967	19 (6)	23 (18)	25 (18)	57 (18)
	CH ₃	H	H	Amitriptyline	-	17 (10)**	17 (10)**	33 (10)**
	CH ₃	H	H	0 38 116	-	17 (8)**	25 (6)**	15 (8)**
	H	H	H	0 38 188	-	42 (8)**	33 (8)**	22 (8)**
	CH ₃	H	H	Promazine	-	21 (8)**	32 (10)**	96 (8)**
	CH ₃	Cl	H	Chlorpromazine	-	3 (6)	83 (5) **	31 (4)**

Hubberg 1a () = number of mice used. * P = 0.01 ** P = 0.001

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TABLE II

Average change of running distance
per mouse in centimeters

Doses in mg/kg i.v.

	0.3	1	3	9
<u>Serotonin antagonists</u>				
LSD 25	5	12 (4)*	26 (4)**	-
Bromo - LSD	-	-6 (4)	10 (4)	-1 (4)
MEL - 491	-	-2 (4)	-1 (4)	-1 (4)
<u>Histamin antagonists</u>				
Cyproheptadine	-	-2 (6)	3 (6)	9 (6)*
Diphenhydramine	-5 (7)	4 (10)**	27 (13)**	7 (7)*
Theridamine	8 (9)*	-8 (9)	5 (9)**	-
<u>Cholinolytics</u>				
Atropine	-10 (4)	-7 (4)	-1 (11)	-7 (26)

** P = 0.001

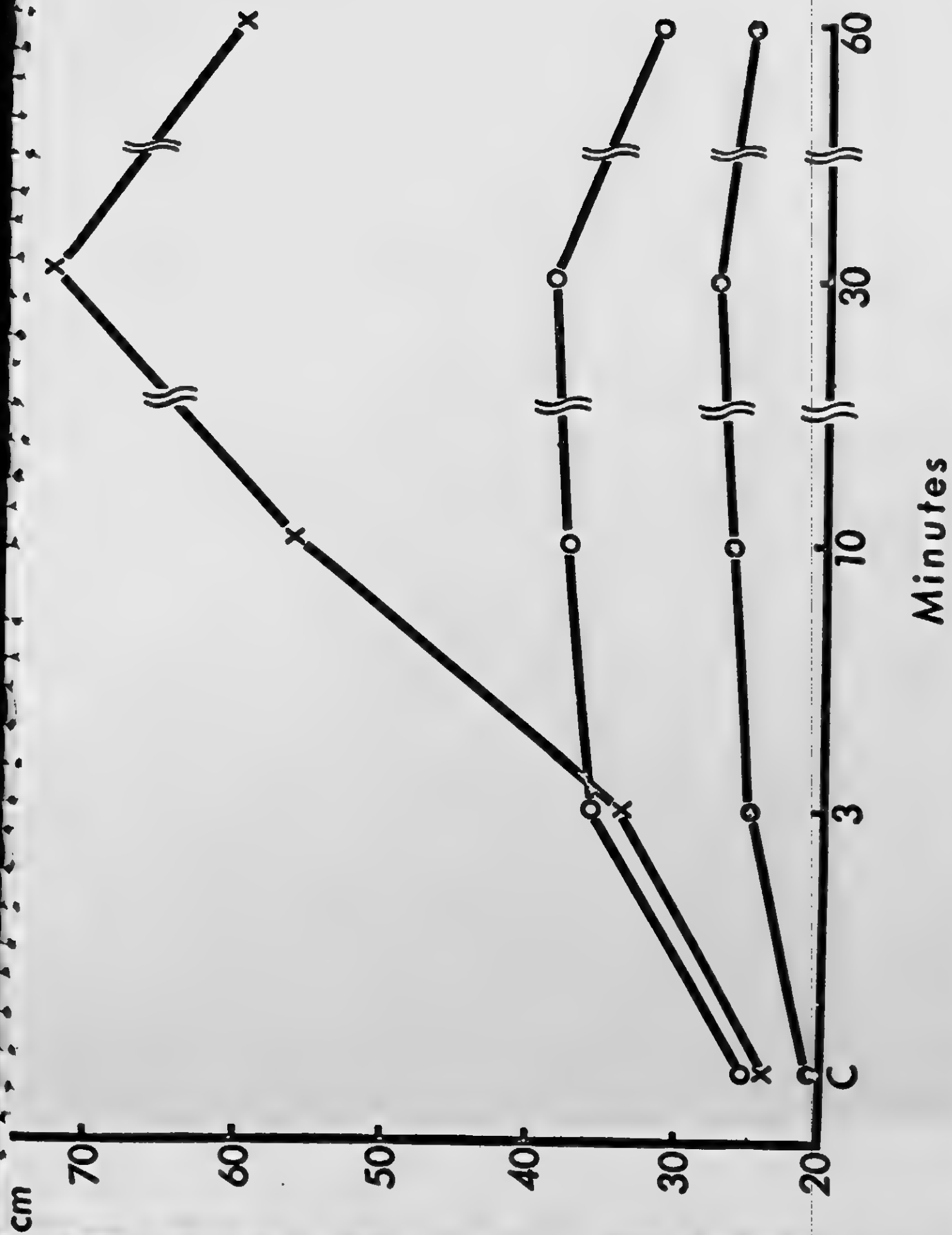
* P = 0.01

Numbers in parentheses - number of mice used.

Fig. 1: Effect of saline (solid circles), imipramine (open circles) and DMI (crosses) on diminution by reserpine of induced locomotor activity in mice.

Ordinate: running distance in centimeters. .

Abcissa: C = control, 120 minutes after i.p. administration of reserpine. Running distances determined 3, 10, 30 and 60 minutes after i.v. injection of test agent into reserpinized mice. Each circle or square in the illustration represents the average of the following number of determinations; saline (14); imipramine (26); DMI (14). The dose of imipramine and DMI was 3 mg/kg i.v.



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Defendant's Exhibit 1A.

(See opposite )

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2,813,857

N-AMINOALKYLATED SUBSTITUTED IMINODIBENZYL DERIVATIVES

Walter Schindler, Riehen, near Basel, and Franz Häfner, Basel, Switzerland, assignors, by mesne assignments, to Geigy Chemical Corporation, New York, N. Y., a corporation of Delaware

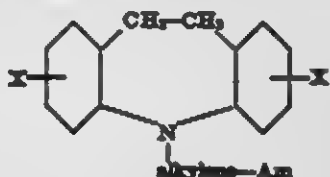
No Drawing. Application August 31, 1955, Serial No. 531,817

Claims priority, application Switzerland September 22, 1954

3 Claims. (Cl. 260-239)

The present invention is concerned with new basically alkylated, substituted iminodibenzyl derivatives which have valuable pharmacological properties and with the production thereof.

Derivatives of nuclear substituted iminodibenzyl have not been known up to now. It has been found that such compounds of the general formula:



wherein

alkylene represents an alkylene radical with 2-6 carbon atoms and 2-4 bridging members

Am represents a low molecular dialkylamino radical or an alkyliminino radical with 5-6 ring members, and X represents a halogen atom

have interesting pharmacological properties, in particular anti-allergic and sedative activity and can be used, among other things, for the treatment of certain forms of mental disorders.

Some quaternary ammonium salts which are derived from the tertiary bases defined above are effective as ganglioplegics.

The new compounds are produced by reacting an iminodibenzyl substituted as defined, in the presence of acid binding agents with a reactive ester of an alcohol of the general formula:



wherein alkylene and Am have the meanings given above. In particular, sodium amide, lithium amide, potassium amide, sodium or potassium are suitable as acid binding agents by means of which it is advantageous to convert the dihalogeno-iminodibenzyl into its alkali salt immediately before the reaction. The reaction is performed advantageously in an inert organic solvent such as, e. g. benzene, toluene or xylene while heating.

In particular the halides can be used as reactive esters of amino alcohols of the general formula:



The following can be named individually: dimethyl-aminoethyl chloride, diethylaminoethyl chloride, methyl-ethylamino ethyl chloride, piperidinoethyl chloride, pyrrolidino ethyl chloride, morpholino ethyl chloride, β -dimethylamino propyl chloride, β -dimethylamino isopropyl chloride, γ -dimethylamino propyl chloride, δ -dimethylamino butyl chloride, ϵ -methyl- γ -dimethylamino pentyl chloride, di-n-propylamino ethyl chloride, methyl isopropylamino ethyl chloride, di-isobutylamino ethyl chloride, di-n-butylamino ethyl chloride or the corre-

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sponding bromides or iodides. 3,7- or 1,9-dibromo-iminodibenzyl, 2,8-, 3,7- or 1,9-dichloro-iminodibenzyl, 3,7- or 2,8-dimethyl iminodibenzyl can be named as nuclear substituted iminodibenzyls.

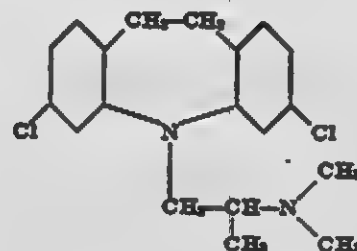
The iminodibenzyls substituted as defined can be obtained, for example from the corresponding substituted diamino-dibenzyls by heating the diphosphates thereof or by heating with polyphosphoric acid. Thus, for example, 3,7-dichloro-iminodibenzyl is obtained from 2,2'-diamino-4,4'-dichloro-dibenzyl by heating with polyphosphoric acid at 220-300°.

Quaternary ammonium compounds result in the usual way from the tertiary aminoalkyl dihalogeno- or dimethyl-iminodibenzyls by the addition of halides or sulphates or aliphatic or araliphatic alcohols, e. g. of methyl iodide, dimethyl sulphate, ethyl bromide or benzyl chloride.

The tertiary bases form water soluble salts with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane disulphonic acid, acetic acid, citric acid, malic acid, succinic acid, tartaric acid, benzoic acid, phthalic acid.

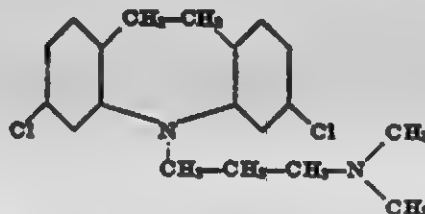
The following examples serve to illustrate the invention; where not otherwise stated, parts are given as parts by weight and their relationship to parts by volume is as that of grammes to cubic centimetres. The temperatures are in degrees centigrade.

Example 1



13.2 parts of 3,7-dichloro-iminodibenzyl are dissolved in 50 parts by volume of abs. benzene. 7 parts of β -dimethylamino propyl chloride in 50 parts by volume of abs. benzene are added, 2.1 parts of sodium amide in toluene are added dropwise within half an hour at 45-55°, the whole is then kept at this temperature for another 2 hours and finally boiled under reflux for 14 hours. The reaction mixture is cooled and shaken out with water. The benzene layer is then shaken out several times, each time with 20 parts by volume of 2 N-acetic acid. The reaction of the united acetic acid extracts is then made alkaline with concentrated ammonia and the base which precipitates is taken up in ether. The ethereal solution is washed with water, dried and evaporated. The residue is distilled in the high vacuum whereupon 5-(β -dimethylamino-propyl)-3,7-dichloro-iminodibenzyl, (5-(β -dimethylamino-propyl)-3,7-dichloro-10,11-dihydro-dibenzo [B. F.] azepine) passes over at 173-175° under 0.004 mm. pressure. The hydrochloride which melts at 254° is obtained with alcoholic hydrochloric acid.

Example 2



13.2 parts of 3,7-dichloro-iminodibenzyl are dissolved in 50 parts by volume of abs. benzene, a solution of 2.2 parts of sodium amide in toluene is added and the whole is boiled for one hour under reflux to form the sodium

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salt. The temperature is reduced to 50°, and a solution of 6.5 parts of γ -dimethylamino propyl chloride in abs. benzene is added while stirring. The whole is stirred for a further 2 hours at 50° and then boiled under reflux for 16 hours. The whole is filtered hot under suction through some charcoal and the filtration residue is thoroughly washed with hot benzene and the united benzene solutions are evaporated in the vacuum. The residue is distilled in the high vacuum. 5-(γ -dimethylamino-propyl)-3,7-dichloro-iminodibenzyl, (5-(γ -dimethylamino-propyl)-3,7-dichloro-10.11-dihydro-5-dibenzo [B. F.] azepine) passes over at 175-179° under 0.01 mm. pressure.

The hydrochloride prepared with alcoholic hydrochloric acid can be recrystallised from acetone. It then melts at 174-175°.

5-(β -piperidino-ethyl)-3,7-dichloro-iminodibenzyl, (5-(β -piperidino-ethyl)-3,7-dichloro-10.11-dihydro-

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5-dibenzo [B. F.] azepine) which boils at 191-193° under 0.007 mm. pressure is obtained in an analogous manner. The hydrochloride thereof melts at 238-240°. Also 5-(β -pyrrolidino-ethyl)-3,7-dibromoiminodibenzyl is obtained in the same way.

What we claim is:

1. A 5-dimethylaminopropyl - 3,7 - dichloro - iminodibenzyl.
2. 5 - (γ - dimethylamino - propyl) - 3,7 - dichloroiminodibenzyl.
3. 5 - (β - dimethylamino - propyl) - 3,7 - dichloroiminodibenzyl.

References Cited in the file of this patent

FOREIGN PATENTS

668,659 Great Britain _____ Mar. 19, 1952

Defendant's Exhibit 1B.

(See opposite )

1214/1-80

215,335

COMMONWEALTH OF AUSTRALIA

PATENT SPECIFICATION

Complete Specification lodged 25th September, 1956.
 Application lodged No. 21,847/56 25th September, 1956.
 Applicant Societe Des Usines Chimiques
 Rhone-Poulenc.
 Actual Inventors Jean Robert and Paul Galliot.

Convention Application,
 (France, 20th October, 1955.)

Complete Specification Published 28th March, 1957.
 Complete Specification Accepted 11th June, 1958.

Classification: 09.6.

No drawing.

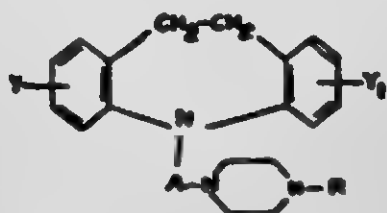
COMPLETE SPECIFICATION.

"Improvements in or relating to iminodibenzyl derivatives."

The following statement is a full description of this invention, including the best method of performing it known to us:—

This invention relates to heterocyclic compounds, and more particularly to new iminodibenzyl derivatives and their production.

According to the present invention there are provided new iminodibenzyl bases of the general formula:



where A represents a saturated straight or branched divalent hydrocarbon group containing from 1 to 6 carbon atoms, R represents a hydrogen atom or a lower alkyl, aryl or aralkyl group, Y and Y₁ are the same or different

ferent and are selected from hydrogen atoms, halogen atoms and lower alkyl, lower alkoxy, aryl and aryloxy groups, and one or more of the carbon atoms of the piperazine ring may carry a substituent in the form of a methyl group, and the acid addition salts, quaternary ammonium derivatives and addition compounds of such bases (for example with 8-chlorotheophylline). By "lower alkyl" and "lower alkoxy" is meant an alkyl or alkoxy group containing not more than 6 carbon atoms.

The new iminodibenzyl derivatives provided by the present invention possess interesting pharmacodynamic properties, are active as antiemetics, "anti-shock" agents, anti-histaminics, spasmolytics, antiepileptics and as potentiators of anaesthetics and analgesics. Where derivatives of the base are concerned the additional groups present should be pharmaceutically acceptable, i.e. they should not impart toxicity to the products. Suitable acid addition salts are the hydrochlorides,

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hydrobromides, citrates and tartrates and suitable quaternary ammonium compounds are the quaternary ammonium iodides and bromides.

According to features of the present invention the aforesaid compounds are prepared by the following methods:—

(1) Reacting an iminodibenzyl of the general formula:



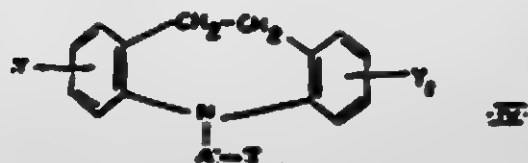
with a halogenalkylpiperazine of the general formula:



wherein X represents a halogen atom, the other symbols being as hereinbefore defined.

This process may be carried out by heating the reactants in the presence or absence of an organic solvent and, if desired, in the presence of an alkaline condensing agent, for example an alkali metal or an alkali metal derivative such as a hydroxide, hydride, amide, alcoholate or organo-alkali metal derivative, and preferably in the presence of sodium hydroxide or sodamine. Instead of the base of Formula III a salt of this base may be employed, but in this case a greater proportion of the condensing agent is preferably employed in order to neutralise the acid of the salt.

(2) Reacting an iminodibenzyl of the general formula:



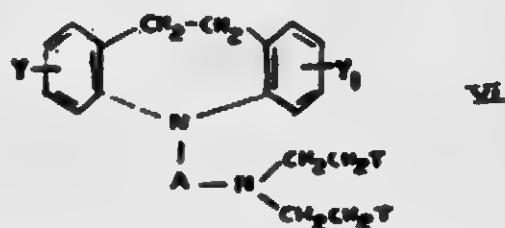
with a piperazine derivative of the general formula:



where T represents the acid residue of a reactive ester (for example a halogen atom or the

residue of a sulphuric or sulphonic ester) and the other symbols are as hereinbefore defined.

(3) Reacting an iminodibenzyl of the general formula:



with an amine of the formula $R-NH_2$, the various symbols being as hereinbefore defined.

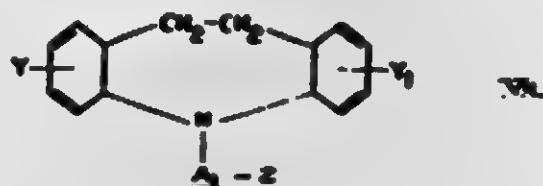
(4) Reduction of compounds corresponding to the products of Formula I in which at least one of the groups A and R is replaced by a group convertible by reduction.

As an example of a convertible group A there may be mentioned the group $-A_1-CO-$.

As an example of a convertible group R there may be mentioned the group $-CO-R_1$.

In these formulae the groups A_1 and R_1 contain one carbon atom less than the groups A and R respectively.

(5) Reduction of an iminodibenzyl of the general formula:



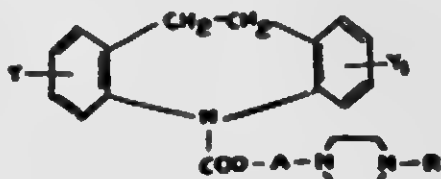
where Z is an aldehyde (CHO) or nitrile (CN) group and the other symbols are as hereinbefore defined, in the presence of a piperazine of the general formula:



where R is as hereinbefore defined.

(6) Hydrolysis of compounds of Formula I wherein the group R represents $-COOR_2$ or $-CON(R_2)_2$, R_2 representing a hydrocarbon group, whereby the compounds for which R represents a hydrogen atom may be obtained.

(7) Heating, to effect decarboxylation, a compound of the general formula:



where the symbols have the meanings hereinbefore defined.

The aforesaid processes may be used separately or in combination. It is also possible to vary the end product by modifying the group R. Thus compounds in which R represents a hydrogen atom may be converted into R-alkyl by alkylation; compounds in which R represents a phenyl group may be converted to R-H by nitrosation and fission; and compounds in which R is a benzyl group may be converted to R-H by reduction.

It will be understood that in all the aforesaid processes except (4) one or more of the carbon atoms of the piperazine nucleus shown may carry a methyl substituent.

The following Examples will serve to illustrate the invention but are not to be regarded as limiting it in any way:—

Examples.

A mixture of iminodibenzyl (6.22 g.), anhydrous toluene (35 cc.) and 95% sodamide (1.43 g.) is heated under reflux with agitation for 1½ hours and a 14.5% solution (42.5 cc.) of 1-methyl-4-(3-chloropropyl)piperazine in toluene is then added over 1 hour. After being heated for 10 hours under reflux, the mixture is cooled, washed with water (2 x 30 cc.) and extracted with normal hydrochloric acid (70, 35 and 35 cc. successively). The acidic solutions are combined, washed with diethyl ether (35 cc.) and then treated with aqueous sodium hydroxide (d = 1.33, 16 cc.). The base is extracted with diethyl ether (3 x 50 cc.) and the combined ethereal solutions are washed with water (30 cc.), dried over sodium sulphate and the ether evaporated on the water-bath. The residue is distilled and there is obtained 5-(2-4'-ethyl-1'-piperazinylethylimino)-dibenzyl (6.04 g.), b.p. 195-198° C./0.4 mm. Hg.

On dissolving the last-mentioned base in alcohol (45 cc.), treating with charcoal and adding a 5.13 normal solution (7 cc.) of hydrogen chloride in alcohol, the dihydrochloride is obtained (7.06 g.), m.p. about 245-248° C. (Koffler.)

By the same general procedure there are obtained

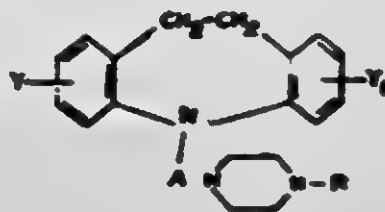
5-(2-4'-ethyl-1'-piperazinylethylimino)-dibenzyl, b.p. 0.3 204-206° C.; dihydrochloride m.p. 239-241° C. (Koffler.)

5-(3-4'-ethyl-1'-piperazinylpropylimino)-dibenzyl, b.p. \approx 198° C.; dihydrochloride m.p. 234-238° C. (Koffler.)

5-(2-methyl-3-4'-methyl-1'-piperazinylpropylimino)-dibenzyl, b.p. \approx 183-188° C.; dihydrochloride m.p. 244-247° C. (Koffler.)

The claims defining the invention are as follows:—

1. Iminodibenzyl bases of the general formula:



where A represents a saturated straight or branched divalent hydrocarbon group containing from 1 to 6 carbon atoms, R represents a hydrogen atom or a lower alkyl, aryl or aralkyl group, Y and Y₁ are the same or different and are selected from hydrogen atoms, halogen atoms and lower alkyl, lower alkoxy, aryl and aralkoxy groups and one or more of the carbon atoms of the piperazine ring may carry a substituent in the form of a methyl group. (20th October, 1955.)

2. Acid addition salts, quaternary ammonium derivatives and addition compounds of the bases claimed in Claim 1 where the additional groups present are pharmaceutically acceptable. (20th October, 1955.)

3. 5-(3-4'-methyl-1'-piperazinylpropylimino)-dibenzyl and its dihydrochloride. (20th October, 1955.)

4. 5-(2-4'-ethyl-1'-piperazinylethylimino)-dibenzyl and its dihydrochloride. (29th September, 1956.)

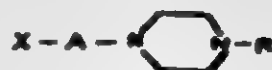
5. 5-(3-4'-ethyl-1'-piperazinypropyl)iminodibenzyl and its dihydrochloride. (25th September, 1956.)

6. 5-(2-methyl-3-4'-methyl-1'-piperazinypropyl)iminodibenzyl and its dihydrochloride. (25th September, 1956.)

7. A process for the production of an iminodibenzyl base as claimed in Claim 1 which comprises reacting an iminodibenzyl of the general formula:

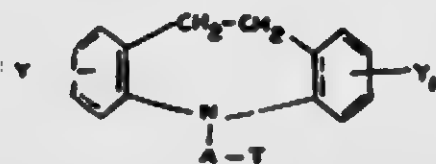


with a halogenoalkylpiperazine of the general formula:



wherein X represents a halogen atom, the other symbols have the meanings assigned to them in Claim 1 and one or more of the carbon atoms of the piperazine ring may carry a methyl substituent. (20th October, 1955.)

8. A process for the production of an iminodibenzyl base as claimed in Claim 1 which comprises reacting an iminodibenzyl of the general formula:



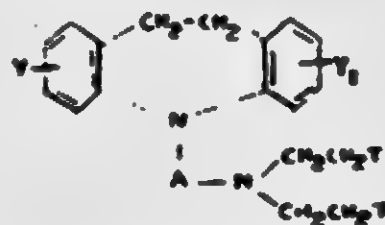
with a piperazine derivative of the general formula:



where T represents the acid residue of a reactive ester the other symbols have the meanings assigned to them in Claim 1 and one or more of the carbon atoms of the piperazine ring may carry a methyl substituent. (20th October, 1955.)

9. A process for the production of an iminodibenzyl base as claimed in Claim 1 which

comprises reacting an iminodibenzyl of the general formula:

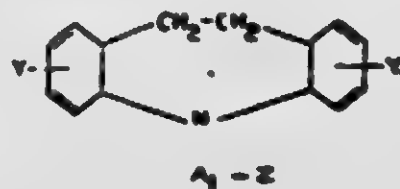


with an amine of the formula $R-NH_2$, where T represents the acid residue of a reactive ester and the other symbols have the meanings assigned to them in Claim 1. (20th October, 1955.)

10. A process for the production of an iminodibenzyl base as claimed in Claim 1 which comprises reducing a compound as claimed in Claim 1 but in which at least one of the groups A and R is replaced by a group convertible thereto by reduction. (20th October, 1955.)

11. A process according to Claim 10 wherein A is replaced by $-A_1-CO-$ or R is replaced by $-CO-R_1$ or both, A and R are so replaced, where A_1 and R_1 differ from A and R in containing one less carbon atom. (20th October, 1955.)

12. A process for the production of an iminodibenzyl base as claimed in Claim 1 which comprises the reduction of an iminodibenzyl of the general formula:



where Z is an aldehyde (CHO) or nitrile (CN) group and the other symbols are as hereinbefore defined, in the presence of a piperazine of the general formula:

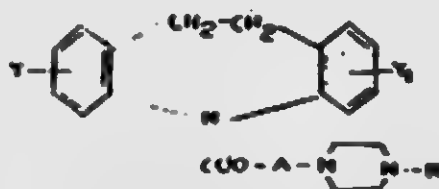


where R is as hereinbefore defined and one or more of the carbon atoms of the piperazine ring may carry a methyl substituent. (20th October, 1955.)

13. A process for the production of an aminodibenzyl base as claimed in Claim 1 which comprises hydrolysing a compound as defined in Claim 1 wherein R is replaced by COOR_2 or $-\text{CON}(\text{R}_2)_2$ grouping where R_2 is a hydrocarbon group. (20th October, 1955.)

14. A process for the production of an aminodibenzyl base as claimed in Claim 1

which comprises heating to effect decarboxylation a compound of the general formula--



where the symbols have the meaning assigned to them in Claim 1 and one or more of the carbon atoms of the piperazine nucleus may carry a methyl substituent. (25th September, 1955.)

15. Processes for the production of compounds as defined in Claim 1 substantially as hereinbefore described. (20th October, 1955.)

9

10

DAVIES & COLLISON,
Patent Attorneys for Applicant.

References:

Serial No.	Application No.	Classification
10,794	11,918/55	09.6
10,795	11,919/55	09.6
10,841	12,030/55	09.6

Defendant's Exhibit 1D.

(See opposite )

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U. S. DEPARTMENT OF COMMERCE
PATENT OFFICE
WASHINGTON

PAPER NO. 13

All communications respecting
this application should give the
serial number, date of filing,
name of the applicant, and
appeal number.

In re application of
Walter Schindler et al

Ser. No. 857,274
Filed Dec. 4, 1959
For NEW N-HETEROCYCLIC
COMPOUNDS

Appeal No. 34-57

Before the Board of Appeals

Wenderoth, Lind, & Ponack for Appellants

RECEIVED

OCT 12 1962

EX-3

Examiner's Answer

This is an appeal from the final rejection of claims
1, 3, 4, 6-13, 16 and 17, all the claims in the application.
No claims are allowed.

A correct copy of the appealed claims appears on
pages 1 and 2 of the appellants' brief.

The references of record relied on are:

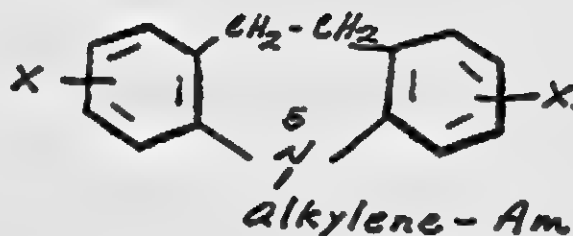
Schindler et al	2,813,857	Nov. 19, 1957	260-239
Austrian Patent	200,578 (4 pp. spec.)	Nov. Mar. 10, 1958	260-239
Australian Patent	215,335 (5 pp. spec.)	June 11, 1958	260-239

The invention is adequately described on page 3
of appellants' brief.

The References

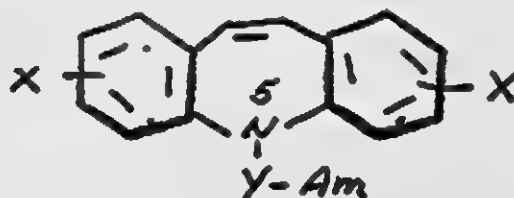
Schindler et al disclose the class of iminodibenzyl

Serial No. 857,274



wherein X represents a halogen atom. These compounds are disclosed to be useful "for the treatment of certain forms of mental disorders".

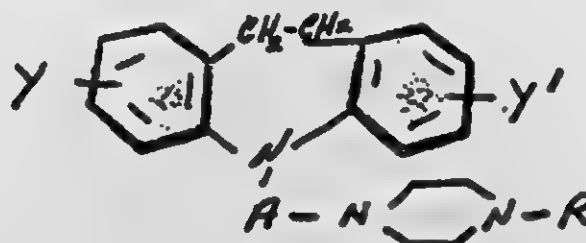
The Austrian patent discloses the class of imino-stilbene compounds:



wherein X represents hydrogen, halogen or the methyl group.

There is no issue raised as to the 5-position in the above references, and so that substituent is not here defined.

The Australian patent discloses the class of imino-dibenzyl compounds:



wherein "Y and Y', are the same or different and are selected from hydrogen atoms, halogen atoms and lower alkyl, lower alkoxy, aryl and aryloxy groups".

The Rejections

All of the claims are rejected as being unduly multiplied.

Claim 1 is rejected as being drawn to a class of compounds which lacks adequate support in the specification as filed.

Defendant's Exhibit 1D.

A. Claims 1, 4, 6, 8, and 11 drawn to 5-aminoalkyl iminodibenzyl compounds stand rejected as being unpatentable over Schindler et al. alone or in view of the Australian patent.

.

The rejection of the selected claims as being unpatentable over the cited art and as not being patentably distinct from the claim of the copending application Serial No. 822,185 may be consolidated and stated in a relatively simple manner. The art and the copending application disclose the unsubstituted and disubstituted compounds of which applicants are claiming the monosubstituted homologues and analogs. In addition the art discloses (the Australian patent) the concept of unsubstitution, mono-and disubstitution in the benzene nuclei of the analogous piperazino substituted compounds. It then would appear advantageous to consolidate the discussion of these rejections.

.

Secondly, there is the teaching of the Australian patent of the equivalency of unsubstituted, mono-, and disubstituted compounds wherein the substituent in the 5 position is the analogous piperazino group. Note that the substituents Y and Y₁ of the Australian patent may be the same or different from hydrogen, halogen and lower alkyl. It is further noted that the alkyl group is further defined as containing not more than 6 carbon atoms. This teaching when taken with the primary references would render the monosubstituted derivatives obvious to one of ordinary skill in the art.

The affidavits submitted by applicants (Paper No. 10) to show superiority of properties of the claimed compounds have not been persuasive of patentability, nor have

Defendant's Exhibit 1D.

the decisions in *In re Lambdy*, 133 USPQ 270; and *In re Petering et al*, 133 USPQ 275. The instant situation is one which is deemed to fall within the rule set forth in *In re Szumski*, 133 USPQ 551 and *In re Prindle et al*, 132 USPQ 282 which hold that:

"Where the change over the prior art is obvious . . . 35 U.S.C. 103 prohibits the grant of a patent. The mere fact that the results attained may be unexpectedly good is not controlling." *In re Szumski*.

.

Defendant's Exhibit 1E.

(See opposite )

U. S. DEPARTMENT OF COMMERCE

PATENT OFFICE
WASHINGTON

PAPER No. 20

All communications respecting
this application should give the
serial number, date of filing,
name of the applicant, and
appeal number.In re application of
Walter Schindler et al.Ser. No. 857,274
Filed December 4, 1959
For NEW N-HETEROCYCLIC
COMPOUNDS

Appeal No. 34-57

Before the Board of Appeals

Wenderoth, Lind & Ponack, for Appellants JAN 21 1962

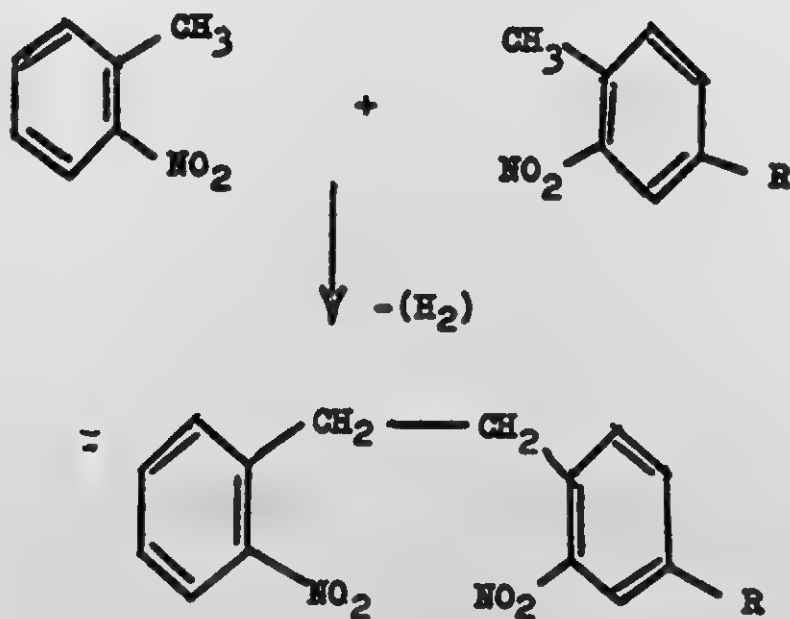
PA.
DIV 5Examiner's Answer
(On Remand)

The reply brief of November 13, 1962, affidavit of November 16, 1962, and amendment of January 14, 1963, have been carefully considered and the points raised are discussed below.

The amendment cancelling claim 1 has been entered since it reduces the issues on appeal. This amendment renders moot the rejection of claim 1 as being drawn to a class of compounds which lacks support in the specification as filed. This rejection is discussed at pages 7-9 of the Examiner's Answer. In addition, this removes the rejection of claim 1 on art but does not affect the rejection of the remainder of the claims.

In respect to the remarks of the reply brief in regard to the paragraph bridging pages 9 and 10 of the Examiner's Answer, the Examiner concurs in applicants' remarks to the extent that on reconsideration this paragraph is deemed to be misdescriptive of the process disclosed herein. This paragraph should be withdrawn from the Examiner's Answer. The Examiner does not, however, concur in the

remarks of the reply brief to the extent that they continue and draw the conclusion that the claimed compounds are rendered patentable. The process disclosed at page 3 of the reply brief when taken with the teaching of the Australian patent which teaches the concept of both the monosubstituted and disubstituted iminodibenzyl intermediates would render it obvious to one of ordinary skill in the art to prepare the monosubstituted compounds by proper selection of the intermediates. That is to say that it would be obvious to one of ordinary skill in the art desiring the monosubstituted iminodibenzyl to react ortho-nitro toluene with the substituted ortho-nitro toluene to form the desired intermediate. This reaction would proceed as follows:



For the above reasons, applicants' arguments that the Australian patent cannot be construed as teaching the concept of the monosubstituted compounds is not deemed persuasive.

Ser No. 857,274

-3-

In respect to the affidavit presented, it is noted that this is not deemed to be persuasive in overcoming the rejections set forth. The arguments are essentially those which were presented during the prosecution and are deemed to be adequately answered by the Examiner's Answer. The rejections are deemed sound and should be affirmed.

Respectfully submitted,

J. Marcus
Acting Examiner

J. Miller
J. Miller/prb

Atty: Wenderoth, Lind & Ponack
Washington Loan & Trust Bldg.
Washington 4, D. C.

Defendant's Exhibit 2.

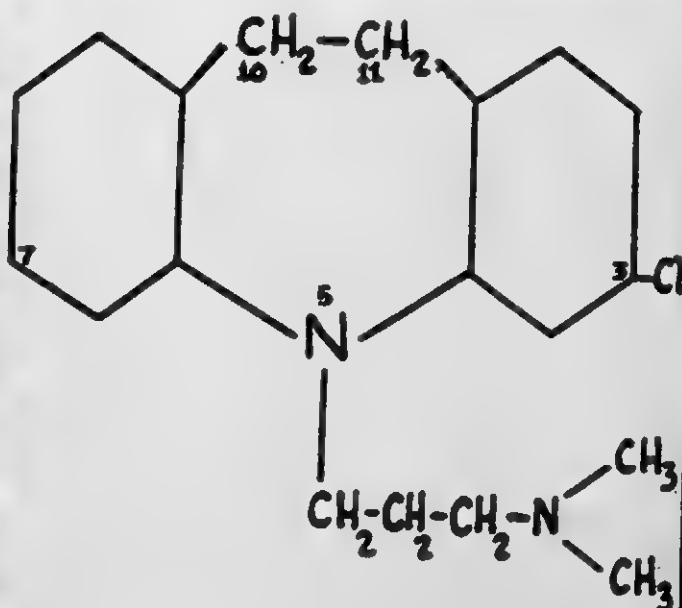
(See opposite **135**)

APPLICATION IN SUIT
CIVIL ACTION NO. 3068-63

SCHINDLER et al

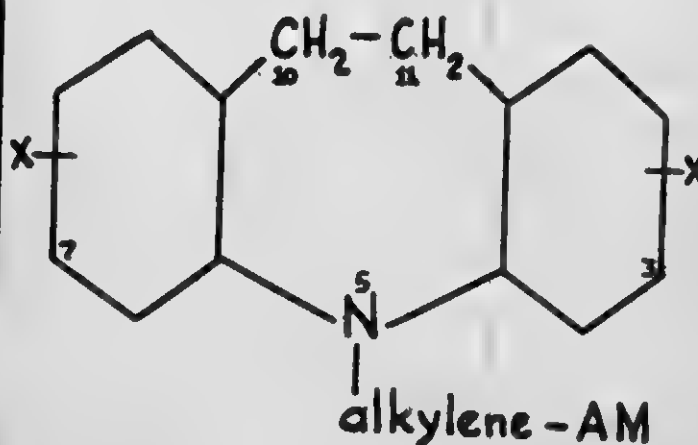
1
CLAIM 8

3-Chloro-5-(γ -dimethyl
amino-propyl)-iminodibenzyl



2
GENERIC DISCLOSURE

Iminodibenzyl
Derivatives



X is a halogen atom

alkylene is an alkylene radical with 2-6 carbon atoms

AM is a low molecular dialkylamino radical or an alkyleneimino radical with 5-6 ring members (pyrrolidino or piperidino radical)

MAILED
AUG 23 1965
FBI



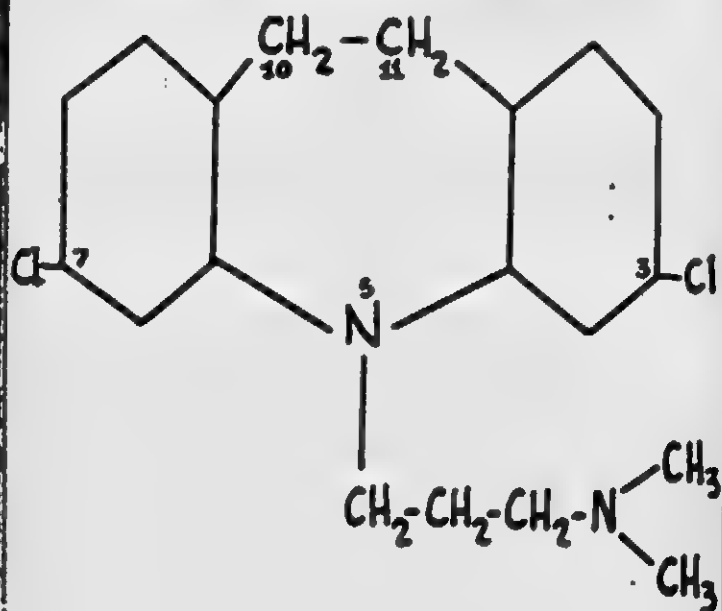
CA 3068-63

U.S. 2,813,857

AUSTRALIAN PATENT
NO. 215,335

3
EXAMPLE 2

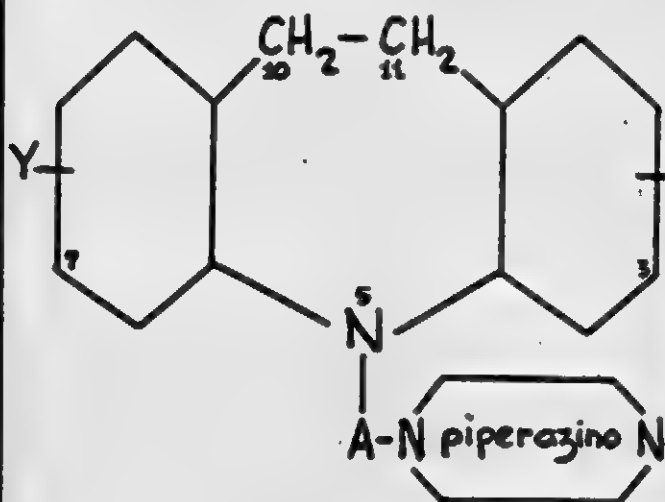
3,7-Dichloro-5 (γ-dimethyl
amino-propyl)-iminodibenzyl



MAILED
AUG 23 1965
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4
GENERIC DISCLOSURE

Iminodibenzyl
Derivatives



Y and Y₁ are the same or different
and may be selected from
hydrogen, halogen, lower alkyl

A may be a saturated straight
divalent hydrocarbon group
with 1-6 carbon atoms

R is hydrogen, lower alkyl,
aryl or araliphatic group

Defendant's Exhibit 3.

(See opposite )

CA 3068-63

FILED

AUG 23 1965

HARRY M. HULL, Clerk

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fortable in spite of the persistence of their basic disorder. The successful home and community adjustment of these patients and those discharged from mental hospitals and the avoidance of relapses necessitating hospitalization are contingent on their treatment by maintenance therapy. Most of these patients will need medication indefinitely.

These drugs are not cures for schizophrenia. The beneficial effects are reflected in reducing the duration and degree of disability and in improving the prospect of a complete remission. These compounds are not a prophylactic against a later relapse. What they do is to lessen tension; as a consequence, the patient becomes less concerned with his symptoms. Delusions may die out for lack of emotional reinforcement or are not verbalized because they do not concern the patient. Hallucinations very often persist but worry the patient less.

SIDE REACTIONS

Side reactions may be divided into (1) normal responses, i.e., those due to the physiologic and neurologic action of the drug and (2) allergic reactions due to hypersensitivity to the compound.

Phenothiazine Derivatives

1. Normal reactions: dryness of the mouth, miosis, weakness and fatigue, aching arms and legs, dizziness, tachycardia, hypotension, constipation, increased dreams, motor restlessness (jitters) and parkinsonian reactions.

2. Hypersensitivity reactions: dermatitis, photosensitivity, jaundice and granulocytopenia.

Risoperidol Derivatives

1. Normal reactions: same as with phenothiazine derivatives plus nasal congestion and diarrhea.

2. Hypersensitivity reactions: rare skin rash.

Management

1. Normal reactions are usually transient, even with continued treatment. If severe, reduce dose or prescribe drugs to counteract them. For weakness and fatigue give Ritalin (methylphenidylacetate) 10 mg. t.i.d. For jitters and parkinsonian reactions give Cogentin (benztropine methanesulfonate) 1 to 2 mg. b.d.

2. Hypersensitivity reactions. (a) Dermatologic reactions are seldom serious. If severe, stop drug and give ACTH. For mild reaction, continue treatment and add antihistamine to medication. (b) Jaundice and agranulocytosis: Stop drug and treat symptomatically. Generally safe to retreat with same drug after jaundice clears. Never retreat a patient who has had agranulocytosis with any phenothiazine derivative.

OFFICE TREATMENT

The office treatment of schizophrenic patients with these drugs will be more successful if the following rules are observed:

1. The dosage must be individualized. Some patients will require very large doses initially.

2. The patient or his relatives should be acquainted with the possible side effects of the drug and should be assured that most of them are commonplace and not serious.

3. Side effects can and should be controlled by reduction of the dosage or by addition of other drugs.

4. The patient should be seen at weekly or bi-weekly intervals during the early stages of his treatment.

5. Therapeutic persistence is imperative. Many of the failures with these drugs can be attributed to either inadequate dosage or the premature termination of treatment.

Depressive Psychoses

METHOD OF LEO ALEXANDER, M.D., *Boston State Hospital and Tufts University Medical School, Boston, Massachusetts*

A depression may be defined as a state of sadness with self-reproach, psychomotor inhibition and disturbances of sleep and appetite.

Nosologic Categories. Depressions are divided into the following nosologic categories: depression, manic-depressive type; involutional depression; and reactive depression. Although manic-depressive and involutional depressions are generally classified among the psychoses, it is important to note that some manic-depressive depressions may be so deceptively mild as to give the impression of neurotic depressions, and some reactive

depressions may be so stormy as to require the type of management demanded by psychoses. Suicidal danger is common to all. There is, however, much more latent and overt anxiety in the neurotic and involutional depressions than in the classic manic-depressive depressions.

TREATMENTS AVAILABLE FOR DEPRESSION

Electroshock is the most effective treatment presently available for depression. It probably

peremesis gravidarum may be insidious and may not be recognized until the patient is in an alarming state, both psychologically and physiologically.

Specific treatment to the etiology of this symptom-complex is much to be desired, but as yet it is not possible. Although there is evidence which implicates psychogenic, nutritional and endocrine elements as causative factors, no completely satisfactory therapeutic agent has yet been obtained. A battery of modalities are available and any one of them may be successful, but it must be admitted that results are uniform only in their lack of consistency. Thus, treatment is empirical; and, therefore, no matter what form of medication is selected, it is imperative that the physician consider the patient as an individual. A careful and thorough elucidation of the patient's background and domestic environment coupled with an abundance of sympathy and understanding often provides the key to successful therapy. The drug being administered should be offered with an optimistic attitude and an assurance of success. To blithely tell the patient, or her husband, that the nausea and vomiting are completely psychologic will only serve to irritate the patient, alienate her from her doctor and intensify her distress. Confidence in her physician will often be the very element which will entirely banish the patient's symptoms or at least make them tolerable. The physician's greatest ally will be time, for most women obtain spontaneous relief from their symptoms within the fourth month of their pregnancy.

THE MILD CASE

If possible, serve the food prepared for the patient, inasmuch as the smell of cooking can be distasteful. Avoid the use of large pills, cod liver oil or other non-palatable preparations.

Upon awakening, before arising, the patient may nibble some unbuttered toast or dry crackers (placed at the bedside before retiring) and wait fifteen or twenty minutes before assuming the erect position.

Frequent light meals—six to seven a day—instead of three heavy meals.

A high carbohydrate diet: toast, biscuits, jams, fruits and vegetables.

Adequate fluid intake of at least two quarts a day in the form of water, ginger-ale, Coca Cola or weak tea.

Antiemetic Agents

Antihistamines. MECHANISM. (1) Direct inhibition of emetic trigger zone in pons and medul-

la, (2) depression of the normal labyrinthine reflex, (3) both (1) and (2).

TYPES. (1) Dramamine (dimenhydrinate), (2) Bonamine (meclizine), (3) buclizine, (4) Marezine (cyclizine). Available as tablets, chewing gum and troches.

DOSAGE. One tablet (25 mg. or 50 mg.) each morning and each night.

SIDE EFFECTS. Drowsiness (can be counteracted by Dexedrine [dextroamphetamine] 1 tablet [5 mg.] each morning).

Vitamins. MECHANISM. To correct possible deficiencies. (1) Pyridoxine (vitamin B₆) 100 mg. I.M. or I.V. daily. (2) Thiamine Hydrochloride 50 mg. I.M. daily.

Combinations of Antihistamines and Vitamins. (1) Bonadoxin (meclizine and pyridoxine), (2) Maredox (marezine and pyridoxine). Dose: One tablet in morning or at night.

Additional Antiemetic Agents. (1) Emetrol (phosphorylated carbohydrate solution). Mechanism: reduces G.I. tract motility. Dose: 1 tablespoon every three hours. (2) Bendectin. Mechanism: Betyl (decreases G.I. tract motility), Decapryn (affects emetic centers), pyridoxine (corrects deficiency). Dose: 2 tablets at bedtime.

Tranquillizers. Because of their bizarre and unpredictable side effects, they probably should be reserved for the more severe cases.

The physician must be alert not to overlook nausea and vomiting due to: peptic ulcer, chronic or subacute cholecystitis, hiatal hernia, esophagitis, drug idiosyncrasies (e.g., to iron preparations), intracranial neoplasm, infectious hepatitis.

THE SEVERE CASE

Hospitalization is mandatory. (A sign for practical use is the finding of acetone in the urine; acetonuria requires hospitalization.)

Nothing by mouth except ice chips.

Correction of dehydration, malnutrition and electrolyte imbalance with 2500 cc. of intravenous fluids every twenty-four hours as 5 per cent glucose in water, isotonic saline, and $\frac{1}{6}$ molar lactate.

Parenteral Sedatives. Phenobarbital 65 mg. (1 grain) three times daily.

Tranquillizers may be used instead of sedatives. Mechanism. Inhibit the emetic centers in brain, relieve anxiety and dread of emesis.

Types. (1) Thorazine (chlorpromazine), (2) Compazine (prochlorperazine), (3) Sparine (promazine), (4) Vesprin (trifluorpromazine).

Boiled or broiled meats (beef, lamb and chicken), at first ground and later unground, may be started. Fish may be added at a later period.

MEDICINAL TREATMENT

Palliative. Analgesics. (1) Camphorated tincture of opium (paregoric) 4 to 8 cc. (1 to 2 drams) p.r.n. every one to two hours for abdominal cramps, diarrhea or tenesmus.

(2) Tincture of opium 0.6 to 1.2 cc. (10 to 20 minims) every one to four hours if symptoms are more severe or if patient cannot take paregoric.

(3) Opium powder 32 mg. ($\frac{1}{2}$ grain) every one to four hours p.r.n. if paregoric or tincture of opium cannot be taken.

(4) When oral intake is not possible, codeine sulfate 60 mg. (1 grain) should be given or,

(5) Demerol (meperidine) 50 to 100 mg. or,

(6) Dilaudid (dihydromorphine) HCl 2.3 mg. ($\frac{1}{4}$ grain) hypodermically every two to four hours until relief is obtained. In severe cases,

(7) Morphine sulfate in 32 mg. ($\frac{1}{4}$ grain) doses with 0.6 mg. ($\frac{1}{100}$ grain) atropine sulfate may be required to bring relief.

Antispasmodics. (1) Tincture of belladonna 1 to 2.3 cc. (15 to 20 minims) every one to four hours together with the opium preparation is useful.

(2) Atropine sulfate orally 0.4 to 0.6 mg. ($\frac{1}{150}$ to $\frac{1}{100}$ grain) every one to four hours may be better tolerated.

(3) Other antispasmodics such as Cantil 25 mg., Monodral 5 mg., Pamine 2.5 mg., Piptal 5 mg., Prantal 100 mg., Pro-Banthine 15 mg. or Tridal (50 mg. Dactil and 5 mg. Piptal) are at times quite helpful.

Sedatives. The administration of 30 mg. ($\frac{1}{2}$ grain) of phenobarbital or one of the other barbiturates in addition to any of the above antispasmodics is frequently of benefit to producing relaxation and pain relief. Bromides, chloral hydrate and tranquilizers, respectively, may help alleviate symptoms in some individual patients more than in others.

Demulcents and Antiseptics. Bismuth, kaolin and calcium preparations in various forms are of value in some cases.

Specific Antimicrobial Therapy. Sulfonamides. The soluble sulfonamides (sulfadiazine, etc.) are effective in many cases.

Antibiotics. The broad-spectrum antibiotics are most effective.* (Determine the most sensitive type.) Until sensitivity is known, it is correct to start with oxytetracycline (Terramycin) or tetracycline, given in 500 mg. doses every six hours during the first day, then in 250 mg. doses every six hours. For children the dose is 50 to 60 mg./kg. This dose should be continued until the temperature becomes normal and stool culture is negative for three successive days.

Furoxone (furazolidone), 10 mg./kg. divided into four doses per day for five days, showed promising results in some epidemics.

CONVALESCENT CARE

In this stage, the patient should receive an adequate, well balanced diet, high in protein and calories, supplemented by high potency vitamins orally or parenterally.

"Smoothage" preparations (methylcellulose) or intestinal lubricants may be given for the reactive "constipation." The patients should be checked periodically, at least for one year, for any sequela and for the possibility that a carrier state has developed.

PROPHYLAXIS

Since bacillary dysentery is spread by the anoral route, hygienic procedures must be taught these patients and their families. Similarly, hospital personnel must be taught the importance of hygienic measures in any area where contact exists with patients suffering from bacillary dysentery. The hands must be carefully cleaned after contact with infected patients or any objects in the patients' environment, since the *Shigella* may be present for a long time on various objects in the room (bed clothes, dishes, eating utensils, etc.). The sick patient is best treated by isolation technique. Adequate observance of standard sanitary measures relating to control of insects, house pets, food handlers, etc., will aid in the control of this disease.

* Attempts to improve the results obtained with tetracycline or Terramycin by giving some patients Chloromycetin and others polymixin B, or combinations of neomycin and sulfadiazine, or streptomycin and sulfaguanidine only demonstrated the superiority of the first two.

Elimination of the Distributing Focus of the Exotoxin. Once clinical tetanus is present, wound management should be directed toward the elimination of the site at which the microorganisms are multiplying and producing toxin. When a wound of entry can be identified, it should be opened, or, if compatible with anatomic considerations, it should be excised. It is obligatory that all foreign bodies and necrotic or grossly infected tissue be removed. The wound should be left open and the area around it infiltrated with 10,000 units of tetanus antitoxin. Although antibiotics do not neutralize preformed toxin, there is evidence that under certain conditions penicillin and oxytetracycline (Terramycin) will prevent multiplication of the microorganisms; for this reason, one or both of these antibiotics may be used as an adjunct to surgical wound management.

Neutralization of Toxin Which Has Not Yet Established an Irreversible Union with Cells of the Central Nervous System. The signs and symptoms of tetanus do not become manifest until there is an interaction between the toxin and the central nervous system. Once this has occurred, it cannot be reversed by antitoxin. This fact dictates one of the aims of therapy: namely, the neutralization of toxin by antitoxin before fixation, or as some believe, change to a secondary toxin, occurs. The amount of antitoxin required is unknown; consequently, there is considerable diversity of opinion concerning the advisable dose and the method of administration. We feel that 100,000 units of antitoxin are sufficient. Ten thousand units are reserved for local injection as stated above and the remainder is divided, approximately equally, between the intravenous and intramuscular routes. No antiserum is given intrathecally, nor is repeated intravenous or intramuscular administration over several days considered necessary. Before any antitoxin is given, the patient must be tested for sensitivity to horse serum. If he is sensitive, he is tested with bovine serum, and if he should be sensitive to both, the antiserum to which he is least sensitive is administered in desensitizing doses. In any event, whether the patient is sensitive or not, one must be prepared to deal with anaphylaxis should it occur.

The Control or Prevention of Muscle Spasm. Measures must be taken to prevent or at least to minimize the distressing muscular seizures which characterize tetanus. The patient should be kept in a quiet, darkened room and all external stimuli minimized. Whatever care and handling are necessary should be done with ex-

treme gentleness. Agents for sedation and muscle relaxation have a definite place in the management of tetanus. The aim of therapy with these drugs is to keep the patient relaxed and to prevent or diminish muscular spasm without making him unconscious and without abolishing his pharyngeal and cough reflexes. A variety of sedatives has been recommended. Phenobarbital is as effective as any. It may be used in doses ranging from 50 to 250 mg. ($\frac{3}{4}$ to 4 grains) for adults (proportionately less for children) given every three or four hours. The amount of drug and the frequency of administration have to be regulated on the basis of individual response. Phenobarbital may be given by any of the usual routes of administration, the one chosen to be determined individually depending upon whether the patient can swallow, upon the degree to which intramuscular or intravenous injections are disturbing and upon the extent to which the patient is being maintained parenterally or by stomach tube or gastrostomy. When the need arises for temporary reinforcement of the basal sedation, an ultra-short-acting intravenous agent such as Pentothal Sodium (thiopental) is employed. To supplement sedation in severe and moderately severe cases, we frequently use mephenesin (3-ortho-toloxyl-2-propanediol). This produces additional relaxation of voluntary muscle without loss of consciousness, since its principal site of action is on the spinal cord. The dosage, given orally, rectally, by nasogastric tube or by gastrostomy, may be varied from 1 to 4 grams every four hours, based upon the individual response, which may be judged by the status of the neck muscles.

Maintenance of Adequate Pulmonary Ventilation. Laryngeal spasm and respiratory compromise due to spasm of the intercostal muscles or diaphragm or involvement of the central respiratory center pose a threat to pulmonary ventilation throughout the course of the disease. Certainly, the first step in dealing with this problem is the uninterrupted presence of an attendant competent to perform the techniques of ventilation. In some circumstances it may be necessary to place the patient in a recovery room or similar constant care unit and to substitute additional sedation for the more ideal surroundings described above. There must be ready for immediate use equipment for tracheostomy, suction, oxygen and artificial respiration. We do not employ, as do some, routine tracheostomy, but reserve its use for cases selected either because of laryngeal stridor or because paralytic

serum. Inhalation of Isuprel solution 1:200 or epinephrine solution 1:100 aerosolized by four or five squeezes of the bulb of a DeVilbiss No. 40 or an Asthmanefrin nebulizer opens the bronchial passages. The patient is instructed to breathe deeply thereafter and to exhale slowly with the lips pursed to expel as much air as possible from the lungs. This breathing and slow expiration is repeated about ten times.

This is a valuable procedure for any asthmatic patient. The increased effectiveness of a prolonged expiration in getting air out of the lung is graphically demonstrated by observing the increase of 200 or 300 ml. in vital capacity registered by a spirometer when such a slow expiration is used as compared with the vital capacity registered after a rapid expiratory blow.

REACTIONS TO DRUGS

METHOD OF ETHAN ALLAN BROWN, M.D., *Boston, Massachusetts*

PREVENTION OF REACTIONS

Except in emergencies, every patient should be questioned as to previous medicines taken, including those not usually looked upon as drugs, namely, acetylsalicylic acid, bromides, sedatives, antihistamines, appetite depressants and tranquilizing agents. Any past ill effects of any type should be noted. Atopic allergy, present or past, immediately indicates that the patient is prone to drug reaction.

In such atopically allergic patients when the choice exists, the least allergenic, not necessarily the newest or most potent or most specific drug, should be prescribed. To prevent the possibility of future reactions, every patient should be told, when it is practicable, what medicines are being prescribed. If ill effects occur, the patient should carry a card noting especially those commonly reactive drugs such as sera, penicillin and the steroid hormones. When feasible or under suspicious circumstances, a small dose can be administered initially both for safety and for "conditioning" purposes. If there is any doubt, a quick-acting antihistaminic agent can also be prescribed twenty minutes before the drug in question is to be taken. An antihistaminic agent can be concomitantly prescribed to prevent the types of reactions which develop slowly. If the drug to be used causes immediate responses, it can, when possible, be preceded by an injection of epinephrine (1:1000) 0.1 to 0.3 ml. given at least ten minutes earlier or, when compatible with an injectable drug, given in the same syringe. Drugs administered subcutaneously can be injected in sites permitting the use of a proximally placed tourniquet.

TREATMENT OF ACUTE REACTIONS

When the reaction is anaphylactic in type, speed of treatment is essential. When the drug

has been administered subcutaneously, epinephrine (1:1000) 0.1 to 0.3 ml. is injected proximal to the site of the injection. A tourniquet is applied between the sites of the two injections. Epinephrine (1:1000) 0.1 to 0.3 ml. is also injected into the opposite arm. Hydrocortisone (100 mg. Solu-Cortef) or an antihistaminic agent such as promethazine hydrochloride (20 to 50 mg. Phenergan) or diphenhydramine hydrochloride (20 to 50 mg. Benadryl) can be given intravenously in the opposite arm. If the reaction affects the lungs, an intravenous injection of aminophylline 0.25 gm. (3½ grains) to which epinephrine (1:1000) 0.05 to 0.1 ml. can be added is administered. When the patient shows signs of recovery (two to ten minutes) but nevertheless continues his reaction in milder degree, intravenous dextrose (500 ml.) with ACTH (20 to 40 units) can then be injected. If the reaction has been caused by penicillin, penicillinase (Neutropen 800,000 units) should be injected as soon as the acute stage is under control, if not earlier if help is available.

If the response is pulmonary, epinephrine (1:100) can also be used by nebulizer or by intermittent positive pressure breathing with oxygen alone or oxygen 40 per cent, air 60 per cent. If need be, a mask and an automatic (Bird Mark 7) intermittent positive breathing apparatus may be life-saving. If the reaction is dermatologic, such as angioedema, a quick-acting antihistaminic agent such as diphenylpyraline hydrochloride (2 tablets of Diafen, 2 mg.) can be given orally followed by the longer acting antihistaminic agents such as chlorcyclizine hydrochloride (Perazil), chlorphenpyridamine maleate (Chlor-Trimeton Repetabs), isothipendyl hydrochloride (Theruhistin) or parabromdylamine maleate (Dimetane). These

juries which result from traffic or industrial accidents, and war. Individual prophylaxis involves the avoidance of asphyxia, or injury at birth, later brain trauma or emotional trauma. There is also the possibility of treating dysrhythmia before the seizures begin, especially if a history of infantile convulsions or other suspicious symptoms is present."

GENERAL THERAPEUTIC MEASURES

It is important to get the epileptic and the community to accept this disease as being one not unlike diabetes or tuberculosis. If this is accomplished, a great gain will have been made in the general management of epilepsy. One treats the epileptic as a whole. In those few cases with cerebral complications such as tumors, infections, etc., steps to alleviate these conditions should be made. The surgical removal of cerebral cicatrices does not guarantee a "cure." For the present, at least, this type of therapy is limited to a few selected cases, usually those which have not responded to medicinal management. In 6 per cent of epileptics alcohol seems to be a definite factor in the production of fits. In this group the interdiction of drinking should be emphasized. In the others moderation can be countenanced.

SOCIAL PSYCHIATRIC FACTORS

It may be stated that there is no adequate management of the epileptic without an attempt to control the social psychiatric factors. This means nothing more than the attempt to educate both the patient as well as his family as to what the diagnosis of epilepsy implies in our present milieu. Attempts should be made to acquaint the patient with the facts about his disease. The need for dissemination of the latest information concerning epilepsy should be emphasized. If they are available the patient should be encouraged to participate in the activities of lay epilepsy organizations. A program of reading concerning epilepsy should be suggested to the patient. One excellent book for both the patient and the doctor is Lennox's *Science and Seizures*. It might well be pointed out to the subject that he usually may not be employed in occupations which expose others or himself to danger, e.g., require him to (1) operate a vehicle, (2) work in high exposed places or (3) manipulate complicated or exposed machinery. It is a common experience that an epileptic invariably becomes a cooperative and grateful patient and not infrequently acts as a spearhead in the attack against social ostracism

by attempting to educate not only himself but his family, friends and even his physician.

The relationship between emotional factors and seizures has long been recognized. Relief by psychologic approaches has been noted by many, and report of occasional cures of epilepsy by psychotherapy are factual and based on sound principles. Passive excommunication of these subjects from the community is traumatizing, as are the other restrictive techniques that have been applied to these patients by their families, friends and well meaning physicians.

DRUG THERAPY

The practicing physician today is faced with a host of anti-epileptic drugs which have literally flooded the market. Even these are relatively few in number compared with the medicinals that are being experimented with by various drug houses and independent researchers.

Some of the more common medicinals include Dilantin Sodium, phenobarbital, Mesantoin, Tridione, Paraldione, Mebaral, Mysoline, Diamox, Gemonil, Celontin, Milontin, Phenurone, Peganone and Mebaroin.

It may be said that the attainment of the ideal medicinal management of the epileptic is rapidly approaching realization. If the next decade proves to be as fruitful as the past one, one might prognosticate that the "magna cum therapa sterilisans" of epilepsy is near at hand.

However, for the present the drugs which the general practitioner needs in the treatment of the average epileptic are few in number. These include phenobarbital, Dilantin (diphenylhydantoin), Tridione (trimethadione), Mesantoin (methyl-phenyl-ethyl-hydantoin) and possibly Mysoline (primidone). The others listed above, as well as the experimental ones, have not yet been completely evaluated. They have been found effective in the hands of some investigators when control with the simpler drugs is not possible.

PRINCIPLES IN THE MEDICINAL MANAGEMENT OF THE EPILEPTIC

Keeping of Records. It goes without saying that in order to evaluate the result of any particular drug adequately it is important to know the seizure frequency. Because the latter may fluctuate, patience must be stressed. A certain treatment may need to be used for many months before its value is established.

Use of the Simplest Drugs. Most adult patients will respond to one or a combination of more



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This action came on for trial February 16, 1965. After reviewing the evidence presented, and considering the briefs the parties were accorded an opportunity to file, the Court has found for the defendant, and against the plaintiffs, and will order that the Complaint be dismissed.

In accordance with Rule 52(a), Federal Rules of Civil Procedure, the Court states its Findings of Fact and Conclusions of Law separately as follows:

FINDINGS OF FACT

1. This is an action brought under Section 145 of Title 35, United States Code, in which plaintiffs Walter Schindler and Henri Dietrich, as applicants of application for patent Serial No. 857,274, filed December 4, 1959, entitled "New N-Heterocyclic Compounds", seek by their complaint a judgment from the Court authorizing the defendant, the Commissioner of Patents, to grant plaintiffs a patent.

2. Plaintiffs withdrew claims 4, 6, 7, 11, 16 and 17 at the trial. Hence, the suit must be dismissed as to these claims.

3. The sole claim in issue is claim 8.

4. The specification of the application in suit describes a class of 3-substituted iminodibenzyl and iminostibene derivatives, which have pharmacological properties, specified as anti-allergic, sedative, spasmolytic, serotonin antagonistic, anti-emetic, adrenolytic, capable of restricting saliva secretions caused by pilocarpine, for the treatment of allergic rhinitis, potentiators of other pharmaceuticals such as anesthesia, and useful in the treatment of certain forms of mental disorders, in particular depressions. The

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compounds are prepared by five alternative processes, but in each process the starting material is a 3-substituted-iminodibenzyl or iminostilbene or derivatives thereof.

5. Claim 8 at issue is directed to a single specific compound within the described class, namely, 3-chloro-5-(γ -dimethylamino-propyl)-iminodibenzyl.

6. The prior art relied upon by defendant in support of the holding of unpatentability of the Patent Office Board of Appeals is as follows:

(a) A United States patent to Schindler et al., No. 2,813,857, disclosing a class of dihalogenated iminodibenzyl derivatives, having utility in pharmacology because of their anti-allergic and sedative properties, and useful also for the treatment of certain forms of mental disorders. Example 2 in the patent shows the preparation of 3,7-dichloro-5-(γ -dimethylamino-propyl)-iminodibenzyl, formed by employing 3,7-dichloro-iminodibenzyl as a starting material.

(b) The Australian patent No. 215,335 disclosing a class of iminodibenzyl derivatives which may be unsubstituted, monohalogen substituted, or dihalogen substituted in the iminodibenzyl nucleus. The compounds are described as possessing interesting pharmacodynamic properties as anti-emetics, anti-shock agents, anti-histaminics, spasmolytics, anti-epileptics, and as potentiators of anesthetics and analgesics.

7. The compounds of claim 8 in suit, Schindler et al. and the Australian patent are structurally closely related.

8. The application at bar, as well as the patent to Schindler et al. and the Australian patents, disclose closely related as well as overlapping pharmacological properties for the classes of compounds disclosed therein.

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9. The evidence does not prove that there was anything unobvious in preparing the monochlorinated iminodibenzyl starting material employed in the preparation of the compound of claim 8.

10. The evidence of comparative tests relating to anti-depressant activity of the compound of claim 8 and that of Example 2 of the Schindler et al. patent is of no legal significance, since it is based on an advantage or property for the claimed compound, which is undisclosed in the application as filed. Nowhere does the original description state that the claimed compound has anti-depressive properties.

11. It would have been obvious to one of ordinary skill in the art to eliminate the 7-chloro substituent from the 3,7-dichloro-5-(γ -dimethyl amino-propyl) iminodibenzyl compound disclosed by Schindler et al., in view of the disclosure of corresponding iminodibenzyl derivatives in the Australian patent wherein those derivatives may be unsubstituted, monohalogen substituted, or dihalogen substituted in the iminodibenzyl nucleus, and in view of the closely related as well as overlapping pharmacological properties disclosed in the two patents.

12. The 3-chloro-5-(γ -dimethylamino-propyl)-iminodibenzyl compound recited in claim 8 in suit would have been obvious to one of ordinary skill in the art at the time plaintiffs filed their application from the combined teachings of Schindler et al. and the Australian patent.

CONCLUSIONS OF LAW

1. An applicant is not entitled to patent protection where he did nothing more than combine teachings avail-

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able in the art in a manner which would have occurred to one skilled in the art at the time the patent application was filed in the Patent Office.

2. Patentability because of unobviousness cannot be based on evidence of an unexpected property in a claimed compound where the application when filed did not expressly disclose that unexpected property for that specific compound.

3. Plaintiffs are not entitled to a patent containing claim 8 of application Serial No. 857,274.

4. The Complaint should be dismissed as to claims 4, 6, 7, 8, 11, 16, and 17.

Dated: June 23, 1965.

JOSEPH R. JACKSON,
United States District Judge.

PART II

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PART II

CIVIL DOCKET

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

Date	Proceedings
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1965

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|----------|---|
| Aug. 23 | Notice of appeal by plaintiff from order 6/23/65; deposit \$5.00 by Smith. (copy mailed to C. W. Moore). filed |
| Aug. 23 | Exhibits #1, 2 and 3 by defendant. filed |
| Sept. 10 | Transcript of proceedings 2/16/65, pages 153. (Reported by Jack Maher) (Plaintiffs copy) filed |
| Sept. 10 | Exhibits 1 thru 6, 6A and 7 of plaintiffs. filed |
| Sept. 13 | Cost bond on appeal of plaintiffs in amount of \$250.00 with United States Fidelity and Guaranty approved and filed. Sirica, J. |
| Sept. 28 | Record on Appeal delivered to United States Court of Appeals; deposit by William A. Smith, Jr. 80¢ |
| Sept. 28 | Receipt from United States Court of Appeals for original papers. filed |

1966

- | | |
|---------|--|
| Apr. 27 | Certified copy order USCA remanding case to USDC with directions to consider evidence described in this order and supplement the record with new findings of fact and conclusions of law and return the enlarged record to USCA. filed |
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Date	Proceedings
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1966

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| May | 2 | Receipt from United States Court of Appeals original record of United States District Court, including transcript and one envelope of exhibits. filed |
| Oct. | 4 | Request of pltffs. for leave to adduce additional evidence; service acknowledged 9-30-66. filed |
| Oct. | 4 | Stipulation of parties for continuance to Dec. 7, 1966. filed |
| Oct. | 6 | Appearance of William A. Smith, Jr., as attorney for pltffs. filed |

1967

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|------|----|--|
| Jan. | 9 | Trial brief by pltffs; c/s 1/6/67. filed |
| Jan. | 11 | Hearing on remand begun; respited until Jan. 12, 1967. (Rep: G. Nevitt) Holtzoff, J. |
| Jan. | 12 | Hearing on remand resumed and concluded; finding for plaintiffs vs defendant. (Findings of Fact, and Conclusions of Law and Judgment to be presented) (Rep: G. Nevitt) Holtzoff, J. |
| Feb. | 2 | Memorandum of deft re: proposed findings of Pltffs, and additional findings of fact proposed by the deft. c/m 2/2/67. filed |
| Feb. | 8 | Findings of Fact and Conclusions of Law. (N) Holtzoff, J. |
| Feb. | 8 | Order declaring plaintiffs entitled to receive patent for invention defined in Claim 8 of patent application 857,274 and authorizing defendant to issue said patent; costs to be assessed against plaintiffs. (N) Holtzoff, J. |

Date	Proceedings
1967	
Feb. 16	Defendants exhibits #4, 5 & 6. filed
Feb. 16	Plaintiffs exhibits #8, 9, 10, 11, 12, 13a, 13b and 14. filed
Feb. 16	Supplemental record on remand delivered to USCA; deposit by William A. Smith, Jr. of 50¢.
Feb. 16	Receipt from USCA for supplemental record on remand and return of original record. filed
Feb. 28	Transcript of proceedings: Jan. 11 and 12, 1967; pages 1-159 (Rep: G. Nevitt—Court's Copy) filed
Mar. 1	Stipulation as to supplemental record. filed
Mar. 2	Supplemental record delivered to USCA; deposit of 50¢ by William A. Smith.
Mar. 2	Receipt from USCA for Supplemental Record. filed
Mar. 3	Stipulation of counsel as to supplemental record. filed
Mar. 3	Transcript of proceedings, 2/8/67 (Rep: Doyne Spencer) (Clerk's copy) filed
Mar. 6	Supplemental Record on Appeal delivered to USCA; deposit of 50¢ by William A. Smith, Jr.
Mar. 6	Receipt from USCA for Supplemental Record. filed
June 13	Certified copy of judgment of U. S. Court of Appeals, Denying motion to dismiss appeal; vacating judgment; and remanding to the District Court. (AC/N) filed

Date	Proceedings
1967	
June 20	Judgment declaring plaintiffs entitled to receive patent for invention defined in Claim 8 and authorizing defendant to issue such patent; costs assessed against plaintiffs. (N) Holtzoff, J.
Aug. 18	Notice of appeal by deft from Order of 6/20/67; copy mailed to William A. Smith, Jr. filed
Sept. 11	Stipulation as to record on appeal. filed
Sept. 11	Return from USCA Original Record; original supplemental record containing reporters transcripts, and original exhibits. filed
Sept. 18	Stipulation withdrawing stipulation filed 9/11/67 and directing the Clerk to transmit the entire record to the United States Court of Appeals. filed
Sept. 22	Record on Appeal delivered to USCA: (Clerk's Fee \$1.55) (U. S. Govt—No Charge)
Sept. 22	Receipt from USCA for Original Papers. filed

TRANSCRIPT OF PROCEEDINGS—January 11 and 12, 1967

[45] The COURT: I will let you do that in your closing argument.

Mr. ARMORE: Thank you, Your Honor.

The COURT: Gentlemen, we are going to take our usual mid-morning recess, but before we do that I want to call the attention of all counsel to two cases that I decided some years ago involving medical patents. *Isenstead v. Watson*, 157 F. Supp. page 7 at page 9, and *Commonwealth Engineering Co. v. Ladd*, 199 F. Supp. page 51 at page 54. Those two set forth some ideas that I have about medical patents.

We will take our usual mid-morning recess at this time.

(Recess.)

The COURT: You may proceed, gentlemen.

Mr. SCHNEIDER: Your Honor, the first witness who plaintiff will present is Dr. Daniel A. Prins.

Dr. Prins testified in the former trial. He was qualified there as a medicinal chemist.

The COURT: I do suggest that you needn't have him repeat what he has already testified to.

Mr. SCHNEIDER: Yes, sir, I will not.

Dr. Prins, please.

Daniel A. Prins—Direct

[46] DANIEL A. PRINS called as witness by Plaintiffs, having duly sworn, was examined and testified as follows:

DIRECT EXAMINATION

By Mr. SCHNEIDER:

Q. Will you please state your full name.

A. My full name is Daniel A. Prins.

Q. Are you the same Dr. Prins who testified in the earlier trial of this action?

A. Yes, I am.

Mr. SCHNEIDER: Your Honor, may we dispense with the qualifications of the witness?

The COURT: Of course. There is no use repeating them.

Q. Dr. Prins, the Patent Examiner and the Board of Appeals have rejected the claim at issue in this case as being obvious over the Schindler patent, No. 2,813,857, in view of Australian patent 215,335. We will apply ourselves to that question.

May I first ask you, in the course of your professional duties as a pharmaceutical chemist have you had occasion to study professional literature?

A. Yes, indeed.

[47] The COURT: He is qualified.

Daniel A. Prins—Direct

By Mr. SCHNEIDER:

Q. Dr. Prins, the Examiner has used the word obvious to describe the relationship of the present invention to the prior patents. What does obvious mean to you?

A. Obvious——

The COURT: No, the Court decides that, what is obvious. I think you better omit those preliminaries. Obvious means that a person reasonably skilled in the art can arrive at the result by the use of his mechanical skill without having to use any inventive faculty. That has been held many, many times.

Q. Can you tell us what qualities of professional literature you would consider as bearing on the question of the obviousness of a disclosure in that literature?

The COURT: You mean this particular disclosure?

Mr. SCHNEIDER: I am talking about general properties now, Your Honor.

The COURT: No, the Court decides that. There is a recent decision of the Court of Customs and Patent Appeals in which Judge Rich made some very significant remarks. He said the way to determine whether a matter is obvious is as though you were taking the prior art and putting it up on the [48] blackboard in front of the inventor and he was working on the subject; would that prior art posted before his eyes as he was working on the subject make the result that he achieved obvious.

So I think that is not a matter of opinion. It may be a matter of opinion whether in the particular instance

Daniel A. Prins—Direct

the result is obvious, but what constitutes obviousness is not a matter of opinion of a witness.

Mr. SCHNEIDER: May I have Defendant's Exhibit 1-A, a copy of the Schindler patent.

The COURT: Do you have another copy? I have to have it before me if you are going to question the witness concerning it.

Mr. SCHNEIDER: Yes, sir.

By Mr. SCHNEIDER:

Q. Dr. Prins, I hand you a copy of the Schindler et al patent which is of record in this case. Are you familiar with this patent?

A. Yes.

The COURT: I assume he is. I think we can omit the preliminaries.

Q. How would you characterize the scope of the disclosure in that patent?

[49] A. The scope I would characterize as being rather narrow.

Q. Have you attempted to calculate the total number of compounds which would be embraced within the disclosures of that patent, Dr. Prins?

A. Yes, I have.

Q. And roughly how many would that be?

A. The total number of species in this patent would roughly be about 145,000.

The COURT: 145,000?

The WITNESS: That is right, Your Honor.

Daniel A. Prins—Direct

By Mr. SCHNEIDER:

Q. Does the Schindler et al patent indicate a preference for any particular group within that rather large number?

A. Yes, it does.

Q. And what preference is that?

A. The preference expressed in the Schindler patent is a preference for chloro as a substituent of the compounds given in that patent.

The COURT: A preference for chloro?

The WITNESS: For chloro being a substituent on the nucleus of the compounds of that patent.

[50] By Mr. SCHNEIDER:

Q. Is there any indication of preference for the number or the amount of chlorine in the nucleus?

A. Yes, it is mandatory to be two chlorine atoms on the nucleus.

Q. Dr. Prins, I now show you the Australian patent, which is Defendant's Exhibit 1-B. Are you familiar with this patent?

A. Yes, I am.

Q. How would you classify the scope of its disclosure, Dr. Prins?

A. The scope of the disclosure is tremendously broad.

Q. Have you attempted to calculate the number of possible compounds falling within the disclosure of the Australian patent?

A. Yes, indeed I have.

Q. Considering now Formula 1 of the Australian

Daniel A. Prins—Direct

patent, we note that this has an iminodibenzyl nucleus and a tail. If we confine our attention only to the nucleus, what values can the substituents Y and Y sub 1 have?

A. The values for the substituents that are defined as Y and Y sub 1 are defined in columns 1 and 2 of the Australian patent. They can be either hydrogen atoms or halogen [51] atoms, they can be lower alkyl groups, they can be lower alkoxy groups, and they can be aryl and aryloxy groups, and it is further defined that they can have these various values accorded to them at the same time and thereby be identical or they can be different.

Q. How many different halogen atoms are there, different types?

A. There are four halogens known to chemistry.

Q. And how many different lower alkyl groups are there?

A. In order to determine that, of course, you have to know what lower alkyl means.

The Australian patent has given a subsidiary definition for the term lower alkyl in column 2 by stating that lower alkyl and lower alkoxy mean an alkyl or an alkoxy group containing not more than 6 carbon atoms.

Q. And assuming that that is what lower alkyl means, how many lower alkyl groups are there?

A. In that case you arrive at 33 meanings which can be accorded to the term lower alkyl.

Q. And lower alkoxy, how many?

A. The same number, namely, 33 meanings.

Q. And what about aryl and aryloxy?

Daniel A. Prins—Direct

[52] A. Aryl and aryloxy are not finite as presented in this patent; in other words, there is an indefinite number.

Q. Are these substituents to be in one single position on the nucleus?

A. No, they can be in all the positions, namely, from 1 to 8, as numbered in the iminodibenzyl nucleus on one of the charts there. That is to say, they can be in 8 different positions.

Q. Now drawing all these things together, Dr. Prins, what is the total number of different substituted nuclei or unsubstituted nuclei comprehended within the scope of the Australian patent? Have you calculated that?

A. The whole patent?

Q. Just in the nucleus.

A. The nucleus comprises about 40,000 species.

Q. Now turning our attention to the side chain or tail, what values are assigned to the symbol A as shown in Formula 1 of the Australian patent?

A. It is stated that A represents a saturated straight or branched divalent hydrocarbon group containing from 1 to 6 carbon atoms.

Q. Does this include any inoperative species?

A. Yes, it does.

[53] Q. Which one is that, or ones?

A. Of the species, those in which A has one carbon between the two adjacent nitrogens, those species for A are inoperative.

Q. How many operative meanings can A have?

A. The number of operative meanings is 103.

Q. In the formula of the Australian patent what values are assigned to R?

Daniel A. Prins—Direct

A. According to the definition in the Australian patent, R represents a hydrogen atom or a lower alkyl, aryl or araliphatic group.

Q. And how many meanings could this embrace?

A. Here we have the same problem. Hydrogen is finite and defined. Lower alkyl has been defined as containing from 1 to 6 carbon atoms. But the meaning of aryl and araliphatic has no finite meaning.

Q. If you exclude those indefinite terms, how many possible variations are there?

A. Well, there is hydrogen that is specific, one. Lower alkyl, from 1 to 6. We had 33. That makes a total of 34 meanings for A.

Q. Are there any other possible variations in the Australian formula?

[54] A. Yes; there is another clause occurring in column 2 of the Australian disclosure and it says that one or more of the carbon atoms of the piperazine ring may carry a substituent in the form of a methyl group.

Q. How many methyl groups may be put into the piperazine ring?

A. Eight.

Q. Do you consider this to be a practical possibility?

A. It may be possible, but not practical. One would start with a monomethyl.

Q. What would you consider to be a practical limitation as to the amount of methyl groups in the ring?

A. One, at most two, I would say.

Q. Well, assuming that there were two methyl groups in the piperazine ring, how many different types of tails are embraced within the broad disclosure of the Australian patent?

Daniel A. Prins—Direct

A. Roughly 24,500.

Q. Well, I believe you said there were roughly 40,000 different nuclei and now 24,000 different tails. How many different total combinations would this amount to?

A. That would give you roughly one billion compounds which all have a piperazine tail.

[55] Q. And if one were to substitute the piperazine ring entirely to the maximum extent contemplated by the Australian patent, how many combinations would there be?

A. Well, far in excess of six billion.

Q. Six billion?

A. Six thousand million.

Q. Dr. Prins, would this vast number of compounds include compounds containing one chlorine atom on the three carbon atom of the nucleus?

A. Yes.

Q. Would it also include compounds having no chlorine atom on the nucleus?

A. Yes.

Q. Would it include compounds having two chlorine atoms on the nucleus?

A. Yes.

Q. Is there any preference expressed in the Australian patent for one type of substituent over the other?

A. None whatsoever.

Q. What, Dr. Prins, would be the most reasonable result of combining the teachings of the Schindler et al patent and the Australian patent?

A. The Schindler et al patent stresses dihalogen and [56] specifically dichloro iminodibenzyl nucleus.

Daniel A. Prins—Direct

By Mr. SCHNEIDER:

Q. Dr. Prins, I show you now Plaintiffs' Exhibit 9 for identification. Can you tell us what this is?

A. This shows the structural formula of a compound, chemical compound, which is obtained when you put the tail of the Australian patent on the nucleus of the application.

Q. By the nucleus of the application you mean the single chloro nucleus which is present in the compound now claimed, is that correct?

[59] A. That is correct.

The COURT: Now as I understand it, the word nucleus you use as covering the three octagons?

Mr. SCHNEIDER: The three rings, sir, is the nucleus.

The COURT: The three octagons?

Mr. SCHNEIDER: That (indicating).

The COURT: These are octagons, aren't they?

The COURT: No, sir, they are two hexagons.

The COURT: Hexagons. I'm sorry.

By Mr. SCHNEIDER:

Q. Have you made this compound shown in Plaintiffs' Exhibit 9, Dr. Prins?

A. Yes, I have.

Q. Has it been screened for anti-depressant activity?

A. It has been screened for anti-depressant activity.

Q. And what was the result?

A. The result was that the property was found not anti-depressant.

Q. What was it?

Daniel A. Prins—Direct

A. The property that was found for this compound was a slight activity as an anti-emetic.

The COURT: May I inquire was this brought out at [60] the prior trial or is this something new?

Mr. SCHNEIDER: This is new, sir.

By Mr. SCHNEIDER:

Q. You testified that this compound had properties as an anti-emetic. Is there any relationship between anti-emetic properties on the one hand and anti-depressant properties on the other?

The COURT: What is the first?

Mr. SCHNEIDER: Anti-emetic, e-m-e-t-i-c.

The COURT: What is that word?

Mr. SCHNEIDER: Contra vomiting, against vomiting, suppressing vomiting.

I asked Dr. Prins to compare —

The COURT: What is the other term?

Mr. SCHNEIDER: Anti-depressant and anti-emetic.

The COURT: What does anti-emetic mean?

Mr. SCHNEIDER: It means inhibiting or suppressing the tendency to vomit.

Q. Is that correct?

A. That is correct.

Q. How is this anti-emetic property related, or is it related in any way to anti-depressant properties?

A. No, I would say on the contrary it is not related [61] to anti-depressant property, not indicative of it.

Q. Does it have a contra-indication?

Daniel A. Prins—Direct

A. I beg your pardon?

Q. Does it have a contrary indication?

A. When in the screen you find anti-emetic property you would not think of possible anti-depressive or anti-depressant activity of that compound, but, rather, of tranquilizing activity for that compound.

Q. Dr. Prins, considering now the total picture that we have taken so far, would it have been obvious, in your opinion, to select the particular compound here claimed from the vast number of possible combinations of the Australian and Schindler et al patents?

A. No, it would not have been obvious.

The COURT: I want to make sure that I draw the proper inference.

Is it your contention that the two prior art disclosures comprise so many ramifications that the selection of any one would require the use of inventive faculty rather than just obviousness?

Mr. SCHNEIDER: Yes, sir, that is part of our case.

The COURT: But I mean on this testimony is that the inference you seek to draw?

[62] Mr. SCHNEIDER: Exactly, sir. And also, of course, that the most natural thing when you put together these two disclosures is to get a compound which has no activity.

By Mr. SCHNEIDER:

Q. Dr. Prins, I show you a copy of United States Patent 2,554,736, Plaintiffs' Exhibit 10 for identification.

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The COURT: Mr. Armore, are you relying on this patent?

Mr. ARMORE: The defendant is additionally relying on this patent as a second—

The COURT: This is the additional patent?

Mr. ARMORE: That is correct, Your Honor, and I had intended to introduce it.

The COURT: Are you relying on this as prior art or as an anticipation?

Mr. ARMORE: As prior art.

The COURT: Very well. That was not cited by the Examiner?

Mr. ARMORE: That was not, Your Honor. This is a second ground of rejection in the case.

The COURT: I say, it was not cited by the Examiner?

Mr. ARMORE: It was not cited by the Examiner and it will be a second ground of rejection.

[63] The COURT: What is the second ground for rejection?

Mr. ARMORE: That the claimed compound is unpatentable over the compound disclosed in this patent.

The COURT: Unpatentable because of obviousness or because of anticipation?

Mr. ARMORE: Because of obviousness.

The COURT: Well, that is not another ground of rejection. That is just additional evidence of obviousness. Very well.

By Mr. SCHNEIDER:

Q. Dr. Prins, are you familiar with this patent?

A. Yes, I am.

Daniel A. Prins—Direct

Q. Dr. Prins, I show you a chart, Plaintiffs' Exhibit 11 for identification. Will you tell us what is disclosed on this chart?

A. This chart gives the structural formula of a compound known as imipramine.

Q. Do you find this compound which is disclosed in Plaintiffs' Exhibit disclosed in Patent No. 2,554,736?

A. Yes, it is there disclosed.

Q. Where do you find that disclosure, Dr. Prins?

A. The disclosure can be found in column 3 of that patent in lines 43, 44 and 45.

[64] Q. What specific information is given there, Dr. Prins?

A. The information stated here is the chemical name of the compound, its boiling point, and the melting point of a derivative called chlorohydrate of it, a salt.

Q. Is the compound specifically named in any of the claims?

A. It is not specifically claimed in any of the claims.

Q. How many other compounds are included within the general disclosure in the patent, approximately?

A. Roughly about 1,000.

Q. Is there any indication in the patent of a compound having a substituted nucleus?

A. Oh, no, there is not.

Q. If one were to desire a substituted nucleus, Dr. Prins, can you give us any idea of the number of choices he would have for making the substitution?

A. Well, the number would be practically limitless because you would have to make your choice first what you wanted to substitute.

Daniel A. Prins—Direct

Q. Is there any suggestion in the patent, Dr. Prins, that a compound with one chlorine atom in the 3 position might have interesting properties?

[65] A. Not in this patent.

Q. Is there anything in the patent which would lead one to substitute a single chlorine atom in the 3 position rather than two chlorine atoms in the 3 and 7 positions?

A. No.

Q. Is there anything in the patent which would indicate that any of the compounds disclosed therein would be useful in the treatment of mental depression?

A. No, there is no such indication.

Q. As a matter of fact, Dr. Prins, do you know whether the compound shown in Plaintiffs' Exhibit 11, the chart, is in fact used in the treatment of mental depression?

A. Are you referring to the compound known as imipramine?

Q. I am.

A. That indeed is used in the treatment of mental depression.

The COURT: It is used?

The WITNESS: It is used, yes, Your Honor.

By Mr. SCHNEIDER:

Q. In bringing a new compound into use as a therapeutic agent for use on human beings, Dr. Prins, are there initial screening tests applied?

[66] A. Oh, yes.

Q. On—

Daniel A. Prins—Direct

A. On animals before you go into man. I mean you couldn't do it any other way.

Q. Are there tests which are regularly performed on animals for us as a guide in determining whether a new compound might have anti-depressant properties with regard to human beings?

A. There are some such tests, yes.

Q. Dr. Prins, I show you Plaintiffs' Exhibit 12 for identification. Can you tell us what this is?

A. Exhibit 12 is a table giving in the lefthand column certain biological activities and in the columns 2 and 3 to the righthand side an evaluation of those properties, biological properties, for two compounds at the head of those columns, namely, the two chloro imipramine and the no chloro imipramine.

The COURT: Then in the last column, that is the compound of the application, is that right?

Mr. SCHNEIDER: No, sir, neither of these compounds in the compound of the application. The dichlorimipramine is the two chlorine compound of the prior art and the imipramine is the no chlorine compound of the prior art.

By Mr. SCHNEIDER:

Q. Dr. Prins, I understand that the properties which [67] are listed under the heading Activity in this chart, which is Plaintiffs' Exhibit 12 for identification, are indicative of probable anti-depressant activity, is that correct?

A. That is correct.

Q. And the numbers—

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The COURT: Suppose you get those properties translated into ordinary English.

Mr. SCHNEIDER: Well, yes, sir, we will try. It's difficult.

The COURT: Those are technical terms which should be explained. Perhaps you can tell me.

Mr. SCHNEIDER: I will ask Dr. Prins this question, but as a preface, what is normally done in these cases, it's impossible to tell whether you have a depressed animal——

The COURT: I want to know what is meant by anti-cholinergic and anti reserpine and anti tetrabenazine. All I want is to get those terms translated into ordinary English.

Mr. SCHNEIDER: Let me just expand a little bit on this. The general procedure is to administer some kind of an outside agent to the animal and then administer the drug that you are testing. Depending upon the opposition or the effect that the drug you are testing has on the drug you have administered, then this can give you a clue to whether you [68] have anti-depressant activity.

The COURT: I understand all that, but I want to know what those words mean.

Mr. SCHNEIDER: Just so long as we start with that from that viewpoint.

By Mr. SCHNEIDER:

Q. Dr. Prins, will you explain what is meant by anti cholinergic activity?

The COURT: No, not explain; just tell me the ordi-

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nary synonym for it in ordinary English. What does it mean?

The WITNESS: Spasmodic.

The COURT: Suppose you tell me.

Mr. SCHNEIDER: Anti cholinergic, I believe, means that it opposes the tendency of an animal to go into spasms when it is——

The COURT: And what is anti reserpine?

Mr. SCHNEIDER: When an animal is administered reserpine it tends to become depressed. Its activity——

The COURT: Is this an anti-depressant?

Mr. SCHNEIDER: The numbers over here are the——

The COURT: The word anti reserpine, is that the same thing as anti-depressant?

Mr. SCHNEIDER: Yes, in a sense, yes.

[69] The COURT: Very well. What is anti tetrabenazine?

Mr. SCHNEIDER: That is also anti-depressant in a first approximation.

The COURT: Is there a distinction between the two?

Mr. SCHNEIDER: These are animal tests. You can't——

The COURT: I mean is there a distinction between the two words?

Mr. SCHNEIDER: Yes, there is, because one uses reserpine and uses tetrabenazine, and on some animals the one has an effect and on the other it does not.

The COURT: But this uses the word activity. What kind of activity does it cover?

Mr. SCHNEIDER: Well, it covers the response of the animal to these drugs.

The COURT: Very well.

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By Mr. SCHNEIDER:

Q. Dr. Prins, considering the numbers on the left-hand side of—the righthand side of the chart which is Plaintiff's Exhibit 12 for identification, if the number is high does that mean that the compound that is in the heading has a tendency toward anti-depressant activity, or does it mean that it has not a tendency toward anti-depressant activity?

A. The higher the numbers in this table the less [70] active the compound.

The COURT: I am afraid I don't understand this. It is not indicated. What do those numbers mean? Do they mean the number of experiments or percentages of results or what?

Mr. SCHNEIDER: They mean the amount of the drug being tested that has to be applied to the test animal to overcome the action of reserpine or tetrabenazine.

The COURT: The amount measured in what?

Mr. SCHNEIDER: In milligrams, I presume.

The WITNESS: These amounts express milligrams per kilogram of the body weight of the animal to get a standardized——

Mr. SCHNEIDER: In other words, the small——

The COURT: As I understand it, these figures represent the number of milligrams that is necessary to attain the result?

Mr. SCHNEIDER: That is right, sir, per kilogram of body weight of the animal.

The COURT: Not milligrams of the drug?

Mr. SCHNEIDER: Milligrams of the drug per kilogram

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of body weight of the animal. The heavier the animal the more you need.

[71] The COURT: I see. In other words, the compound shown in the last column requires a much smaller quantity of the compound to attain the same result than the compound shown in the next-to-last column, is that correct?

Mr. SCHNEIDER: Precisely, sir.

The COURT: Now I understand this. This is a bit blind.

Mr. SCHNEIDER: Yes, sir, I realize that.

The COURT: Very well, I think you have covered that.

Mr. SCHNEIDER: I notice that I have not actually asked that these be accepted in evidence.

The COURT: Let them be admitted.

Mr. SCHNEIDER: 9, 10, 11, 12.

(Plaintiffs' Exhibits Nos. 9, 10, 11 and 12 for identification were received in evidence.)

By Mr. SCHNEIDER:

Q. Dr. Prins, from your experience as a pharmaceutical chemist can you make any observations as to whether a change of structure such as one would have by the introduction of a single chlorine atom into the molecule of a compound would have any effect on physiological properties?

A. My experience as a medicinal chemist has taught me [72] that you cannot predict. In other words, you cannot predict the effect of a given change in structure on the biological properties of the compound that will result.

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The COURT: You mean you have to experiment with it?

The WITNESS: Well, you have to find out.

The COURT: You have to find out, is that it?

The WITNESS: You cannot say, I do this and this will be the result.

By Mr. SCHNEIDER:

Q. Dr. Prins, referring to Plaintiffs' Exhibit 12, on the basis of those figures would you have expected that the introduction of chlorine into the iminodibenzyl nucleus would increase or decrease its anti-depressant properties?

A. From the table in Exhibit 12 the effect of the introduction of chlorine into the molecule is one of suppressing its property or activity, losing it.

Q. Which property or activity?

A. Anti-depressant, as in this table.

Q. From your experience as a pharmaceutical chemist, Dr. Prins, can you make any observations with respect to the effect on pharmaceutical properties of small changes in the structure of chemical compounds?

A. Well, one cannot predict what will happen when one [73] makes small modifications in structure.

Q. Dr. Prins, I show you Plaintiffs' Exhibit No. 13 for identification. Can you tell us what this is?

A. Exhibit 13 represents a table containing several columns, which I drew up in trying to compare various known medicinal compounds as to their activities and their structures. The compounds are grouped in pairs and the structural formulae of these compounds are given in the first column.

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The second column indicates the names of the compounds.

The third column, headed classification, gives the biological or medicinal property or use of those compounds.

Then columns four and five, which are headed difference between, on the one hand, compounds, and on the other hand, activities, states what these differences are.

And the column headed references gives the literature reference to those compounds.

Q. Do I understand from this chart, Dr. Prins, that small changes in structure can result in changes in properties one of which is the reverse of the other?

A. Yes, indeed.

The COURT: I don't think you have to demonstrate that a slight change might make a tremendous difference in the [74] result. The Court will take that for granted.

By Mr. SCHNEIDER:

Q. Considering the structures of the compounds disclosed in the Schindler patent and the Australian patent and given the structure of the compound of claim 8, what would you have expected its properties to be?

A. Impossible to say. Knowing from the properties of the Schindler compound that chlorine is adverse, I would not have expected these compounds to be very useful, the claim 8 compound, that is.

Mr. SCHNEIDER: I think that is all, Your Honor.

The COURT: Mr. Armore.

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CROSS-EXAMINATION.

By Mr. ARMORE:

Q. Dr. Prins, the Schindler et al patent clearly discloses the two chlorine compound that corresponds to the one chlorine compound which is the compound of claim 8 in suit, is that correct?

A. In a sense, yes, because the two chlorines in the Schindler patent do not have fixed positions.

Q. Do you have a copy of the Schindler patent before you?

A. Yes, I have it before me. Are you referring to [75] the patent 857?

Q. I am referring to Schindler et al Patent 2,813,857.

A. Thank you very much. Yes, sir.

Q. I direct your attention to example 2 in that patent. In example 2 does that patent expressly disclose the two chlorine compound corresponding to the one chlorine compound of claim 8 and also show the structural formula of that compound?

A. It does.

The COURT: Would you simplify your question? Just repeat your question in a simple way. Does it disclose what?

Mr. ARMORE: Does example 2 disclose the two chlorine compound—

The COURT: Very well. Then stop. That is the question.

Where is example 2 in the patent?

Mr. ARMORE: It is on the first page at the bottom of column 2. There is a structural formula which is

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the structural formula of the two chlorine compound.

The COURT: You may answer, Doctor.

The WITNESS: It does.

The COURT: That does disclose two atoms of chlorine?

The WITNESS: It discloses two atoms of chlorine, [76] yes, Your Honor. It is the compound on the chart.

By Mr. ARMORE:

Q. And those two atoms of chlorine are specifically situated in the 3 and 7 positions of the iminodibenzyl nucleus, is that correct?

A. That is correct.

Q. I refer you to the Australian patent. Do you have a copy of that, Dr. Prins?

A. I do.

Q. In column 1 of the Australian patent does that patent disclose a class of compounds which have an iminodibenzyl nucleus and which compounds are closely related, therefore, to the——

The COURT: Don't argue in your question; just ask a simple question. Then you can make the argument.

Q. Does the Australian patent in column 1 disclose, by structural formula, a class of compounds which have the iminodibenzyl nucleus?

A. Yes, it does.

Q. Does that structural formula in the patent indicate that the iminodibenzyl nucleus may be either unsubstituted, monohalogen or dihalogen substituted?

A. The iminodibenzyl in the Australian patent may

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be [77] unsubstituted, monosubstituted and disubstituted.

Q. Is the answer to my question yes?

A. No. Yes, it may be dihalogen substituted and monohalogen substituted and unsubstituted.

Q. Then is the answer to my question yes?

A. Yes, sir.

Q. To a chemist would halogen include and also suggest chlorine?

A. Yes.

Q. You have testified that the Australian patent actually encompasses a very large class of compounds, is that correct?

A. That is correct.

Q. Therefore, would it be correct to say that the Australian patent discloses a very large class of compounds having an iminodibenzyl nucleus which may be unsubstituted, monohalogen substituted or dihalogen substituted?

A. Would you restate that?

The COURT: Suppose we have the question read.

(The Reporter read the last question.)

A. Yes.

Q. As a skilled and searching synthetic organic chemist, if you were primarily contemplating the dichlorine [78] compound of the Schindler et al patent at your desk and not in the laboratory, would the Australian patent at least suggest the corresponding monochloro compound?

A. No.

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The COURT: You don't expect any other answer, do you?

Well, we will take our usual luncheon recess at this time.

(At 12:30 p.m. trial stood in recess, to reconvene 1:45 p.m.)

AFTERNOON SESSION

The COURT: Mr. Armore, you may proceed.

By Mr. ARMORE:

Q. Dr. Prins, does the Schindler et al patent and the Australian patent both disclose important pharmacological properties for the compounds disclosed there?

A. Could I have the patents again to refer to?

The COURT: Do they?

Mr. ARMORE: They do, Your Honor.

[79] The COURT: Then don't ask him. The patents speak for themselves.

Where do they disclose that?

Mr. ARMORE: In the patents.

The COURT: Then you can argue that in your summing up.

By Mr. ARMORE:

Q. In view of the fact that both patents disclose important pharmacological properties and both patents disclose closely related compounds, would it be

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apparent to you as a skilled chemist, viewing the two chlorinated Schindler compound, that there may also exist the concept of a one chlorinated compound?

A. No.

The COURT: Mr. Armore, I wish you wouldn't ask the plaintiffs' witnesses a question whether they think a think is obvious. Naturally they won't say yes because if they said yes their client would be out of court. I think it is just a waste of the Court's time to do that.

Mr. ARMORE: I'm sorry, Your Honor.

The COURT: You can't expect any other answer.

Mr. ARMORE: I will proceed from there.

Your Honor, the plaintiff's attorney has introduced [80] into evidence the patent that the defendant was going to introduce into evidence.

The COURT: Well, it is in evidence.

Mr. ARMORE: Would there be any point in my introducing it in evidence on behalf of the defendant?

The COURT: No; either side can use any exhibit in evidence, irrespective of who introduced it. You can use it just as much as though you introduced it yourself.

Mr. ARMORE: I simply wanted to make it clear on the record that the defendant had intended to introduce this patent into evidence.

The COURT: You have made it clear to the Court.

Mr. ARMORE: I have a photocopy of an article by Kuhn appearing in a Swiss publication, which is in German but has an English summary at the back. I would like to have this article marked as Defendant's Exhibit for identification.

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The COURT: Are you offering it in evidence?

Mr. ARMORE: I am going to offer it into evidence.

The COURT: You have shown it to Mr. Smith and Mr. Schneider?

Have you seen it, gentlemen?

Mr. SCHNEIDER: Yes, sir.

Mr. SMITH: Yes, Your Honor.

[81] The COURT: Let it be admitted.

(Defendant's Exhibit No. 4 was marked for identification and received in evidence.)

Mr. ARMORE: May I point out to the Court that one page in German of the article is missing from this exhibit, but since we are relying upon the last page, which is in English, the summary——

The COURT: In the first place, I don't know German, and in the second place even if I did, I don't think I would be authorized to take judicial notice of it because the official language of the Court is English.

There is no translation here, is there?

Mr. ARMORE: I am merely relying upon the last page, which gives a summary in English as part of the article.

The COURT: Well, I will consider that as evidence. Now just what part of the summary are you referring to?

Mr. ARMORE: All of the summary, Your Honor, starting in the middle of the last page, the first column.

The COURT: But what specific statement are you referring to? You mean it is all relevant?

Mr. ARMORE: The first three paragraphs are particularly relevant, the fourth paragraph has some relevancy, too.

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[82] The COURT: Well, for what point are you introducing this?

Mr. ARMORE: I am introducing this to show that it was well known in the art, at least by 1957, that the nonchlorinated compound imipramine was well known to have antidepressant properties.

The COURT: That what kind of compounds?

Mr. ARMORE: The non-chlorinated compound imipramine.

The COURT: Is the compound in the present case in that——

Mr. ARMORE: No, Your Honor, it is not. The present compound has one chlorine atom.

The COURT: And this is without chlorine?

Mr. ARMORE: This is without any chlorine.

I have another copy of this.

The COURT: You are through with the cross-examination?

Mr. ARMORE: No, Your Honor, I am not. I wanted to show this to the witness.

The COURT: Very well.

Mr. ARMORE: I have a copy of this I will hand to the witness and I will ask the witness to look at the summary [83] on the last page.

By Mr. ARMORE:

Q. Dr. Prins, does this confirm your earlier testimony that imipramine is known to have anti-depressant properties?

A. Oh, yes.

Q. Does this also indicate on the same page, in para-

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graph 3, that this compound is effective in many cases of schizophrenia?

The COURT: Where does it say that?

Mr. ARMORE: In the third paragraph under summary.

The WITNESS: Partly.

The COURT: I am reminded of the saying that a little learning is a dangerous thing, but I have heard so much psychiatric testimony in various cases and I was under the impression that schizophrenia could not be cured by medicine. Apparently I am wrong, I have a wrong impression.

Mr. ARMORE: I offer that article by Kuhn into evidence, Your Honor, as Defendant's Exhibit 4.

The COURT: It is in evidence.

Q. Dr. Prins, you have testified that in a number of cases you have found that compounds which have had small structural changes have resulted in compounds which have entirely different biological properties?

[84] A. Yes.

Q. Would you be surprised if you found that you had made a small change in a chemical compound and it did not have substantially different biological properties?

A. Not necessarily.

Q. Would it not more generally be the case that where a small change is made in a compound which exhibits biological properties, that that small change generally or frequently will not result in radical biological changes?

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The COURT: Those are generalities, Mr. Armore. We all know sometimes it happens, sometimes it doesn't happen.

Mr. ARMORE: My point, Your Honor, is that more usually it does not happen.

The COURT: That makes no difference. The question is whether it happened here.

Mr. ARMORE: May I have a copy of Plaintiffs' Exhibit 8, please?

By Mr. ARMORE:

Q. I hand you Plaintiffs' Exhibit 8, Dr. Prins. You have testified that this compound was tested and was found not to exhibit anti-depressant properties, is that correct?

A. Yes, as stated——

The COURT: Just answer yes or no.

Read the question, please.

[85] (The Reporter read the last question.)

The WITNESS: Yes.

By Mr. ARMORE:

Q. Did you make those tests yourself?

A. No, sir.

Q. Were they made under your supervision or direction?

A. No, sir.

Q. Then this testimony which you have given is merely based on what somebody has told you, is that correct?

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A. The pharmacologist reports to the chemist. That is where I get the information from.

Mr. ARMORE: I would object to the admission of this evidence.

The COURT: I will overrule the objection. This is a matter of scientific opinion, in a way, and this witness is a highly qualified expert.

Q. Are you in a position to state the conditions under which the tests were performed as a result of which this conclusion was drawn with respect to Plaintiffs' Exhibit 8?

A. The information was an opinion given by the pharmacologist doing the various tests and this information, to me, was sufficient to indicate that this compound was not of interest to follow up further.

Q. Would the same apply to Plaintiffs' Exhibit—the compound of Plaintiffs' Exhibit 9? Would you give the same answer to the same question with respect to the compound of Plaintiffs' Exhibit 9?

A. Yes.

Mr. ARMORE: May I have Plaintiffs' Exhibit 12, please.

By Mr. ARMORE:

Q. Would the same answer apply to the conclusions stated on Plaintiffs' Exhibit 12?

A. With respect to the quality of the compounds tested?

Q. With respect to whether or not you personally

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made the tests or the tests were made under your direct supervision or instructions.

A. No, these figures were reported in the way I stated before, by the pharmacologist to the chemist.

Q. Do you have the clinical or laboratory data on which the conclusions indicated by Plaintiffs' Exhibits 8, 9 and 12 were based?

A. Not with me, no.

Q. Did you have them in your possession at any time?

A. Well, I looked at them before I drew up the table, yes, and discussed with the pharmacologist what the meaning of [87] these reports was.

Q. Are you able to state how many animals were tested in each category?

A. These are details of pharmacological laboratory experimentation which are outside my field.

Q. These are details which you do not know, is that correct?

A. Well, I can find them on the original reports from the pharmacologist.

The COURT: Aren't we going a little far afield, Mr. Armore? This case relates to the one particular substance in claim 8. The exhibits involve other compounds.

Mr. ARMORE: They do, Your Honor, yes. I just wanted to establish that whatever——

The COURT: I understand, but let's not spend too much time on side issues.

Mr. ARMORE: Yes, Your Honor. I have finished that part.

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The COURT: Go ahead with the next question.

By Mr. ARMORE:

Q. Dr. Prins, given the concept of the one chlorinated compound which is claimed in suit, if you were asked to prepare that compound from the non-chlorinated compound imipramine [88] prior to 1958 would you, as a skilled chemist, have known how to prepare the one chloro compound?

A. No.

Q. Why not?

A. Because one first would have to invent a route, a process for making the compound.

Mr. ARMORE: Your Honor, I have a chemical textbook here, The Chemistry of Organic Compounds, by Conant and Blatt. I have photocopied the title page, the reverse of the title page, which shows the date of the publication, which is quite old, and certain pages of this textbook. I would like to have this photocopy marked for identification as Defendant's Exhibit 5.

The COURT: Have you shown a copy to Mr. Smith and Mr. Schneider?

Mr. ARMORE: No, I haven't yet, but I will give them a copy now.

This is a classical chemical textbook.

The COURT: Very well, let it be admitted.

(Defendant's Exhibit No. 5 was marked for identification and received in evidence.)

Mr. ARMORE: I have another copy that I hand to the witness and I ask him to check the photocopies

Daniel A. Prins—Direct

against [89] the textbook to see whether they are correct.

The WITNESS: They are.

By Mr. ARMORE:

Q. Isn't it conventional in organic chemistry if you want to chlorinate a non-chlorinated organic aromatic compound, that you simply treat it with chlorine in the presence of a catalyst?

The COURT: Mr. Armore, we are not dealing with a process claim; we are dealing with a product claim here.

Mr. ARMORE: Yes, Your Honor, I realize that, and I believe that any testimony or evidence that has been introduced about the process is irrelevant; however, at the original trial certain testimony was introduced attempting to show that the process—that one skilled—

The COURT: I am trying this case now.

A process may be invention and may not be, and a product may be invention and may not be invention. The two don't necessarily go together.

Mr. ARMORE: I agree, Your Honor.

The COURT: Of course you do because that is elementary. I am not saying anything that is of any particular importance.

Therefore, it seems to me to be irrelevant to show [90] how easy it is to change one compound into another by adding something. The question is not how easy it is to make the change, but what result you accomplish by making the change.

Daniel A. Prins—Redirect

Mr. ARMORE: Yes, Your Honor. I will be satisfied by merely offering Defendant's Exhibit 5 into evidence.

The COURT: I have admitted it in evidence. I notice it is a textbook by a very eminent gentleman.

Mr. ARMORE: Yes, Your Honor, it is Conant, who used to be a professor at Harvard.

Under the circumstances, I will terminate my cross-examination.

Thank you.

The COURT: Do you have any redirect?

Mr. SCHNEIDER: Just one.

First of all, I would like to introduce Plaintiffs' Exhibit 13 for identification into evidence. I don't believe that is in yet, 13-A and -B.

The COURT: Let it be admitted.

(Plaintiffs' Exhibits Nos. 13-A and 13-B for identification were received in evidence.)

REDIRECT EXAMINATION.

By Mr. SCHNEIDER:

Q. Dr. Prins, defendant has discussed the compound [91] imipramine, which is the no chlorine compound. What would be the normal result or the most obvious result of combining the teachings of the patent or the article which shows imipramine and the article which shows the Australian formula?

A. That would be to put the tail of the Australian formula on the nucleus of the imipramine, which is no chlorinated iminodibenzyl.

Daniel A. Prins—Redirect

Q. I show you now Plaintiffs' Exhibit 14 for identification. I ask you, Dr. Prins, what is the compound shown on that——

The COURT: How is this redirect examination? What is the purpose of this?

Mr. SCHNEIDER: Well, sir, simply to show if we take this imipramine, the non-chlorinated compound, and we add it to the tail of the Australian patent, what we get is a——

The COURT: Very well, you may ask the question. I see.

The WITNESS: Will you state your question again, please?

The COURT: Will you read the question, please?

(The Reporter read the last question.)

Q. —on that Exhibit No. 14?

A. That is the compound that results from the [92] combination of the nucleus of imipramine and the tail of the Australian patent.

Q. Has this been screened for anti-depressant activity?

A. It has.

Q. And with what result?

A. It was found to be ineffective, inactive.

Mr. SCHNEIDER: I offer Plaintiffs' Exhibit 14 in evidence.

The COURT: Let it be admitted.

(Plaintiffs' Exhibit No. 14 for identification was received in evidence.)

Daniel A. Prins—Redirect

The COURT: Is there anything more?

Mr. SCHNEIDER: Yes, just one more thing.

By Mr. SCHNEIDER:

Q. Dr. Prins, I show you now Defendant's Exhibit 4, which is the Kuhn article. Is there anything in this disclosure, Dr. Prins, which would suggest to you the use of the monochloro compound presently claimed for the treatment of mental depression?

A. No, it would not.

Q. Do you find anything in this disclosure which would indicate that the monochloro compound might not be a useful drug in the treatment of depression?

[93] A. No.

Mr. SCHNEIDER: I believe that is all, Your Honor.

The COURT: You may step down.

Mr. SCHNEIDER: Your Honor, we have now two witnesses who are physicians. One is a citizen of Switzerland, the other a citizen of France. Neither one of them is fluent enough in English to testify in English.

The COURT: I am sure they are, but, however, if they feel more comfortable in using an interpreter they can testify through an interpreter. I have found that Europeans are so much better linguists and sometimes I feel ashamed of myself.

Mr. SCHNEIDER: Yes, sir, I understand the feeling. We will need, then, an interpreter sworn.

The COURT: Do they both speak French? Do you need a French interpreter?

Mr. SCHNEIDER: Yes, sir.

Gaston Garonne—Direct

The COURT: The reason I asked that is in some parts of Switzerland German is the prevailing language.

I think we better swear the interpreter first.

Mr. SCHNEIDER: Mr. George Weissglas is our interpreter.

(The Deputy Clerk administered the Interpreter's Oath to the Interpreter, Mr. George Weissglas.)

[94] Mr. SCHNEIDER: We will first call Dr. Gaston Garonne.

GASTON GARONNE, called as a witness by Plaintiffs, having been duly sworn, was examined and testified through the interpreter as follows:

Mr. SCHNEIDER: Your Honor, Dr. Garonne is the affiant in an affidavit which is in the record, in the Patent Office record, and that affidavit recites his qualifications at some length. May we dispense with the qualifications?

The COURT: Yes, indeed. Now I do want to locate his affidavit in the file wrapper, please.

Mr. SCHNEIDER: In my copy it is on page 78 of the file wrapper.

The COURT: Yes, I have it.

DIRECT EXAMINATION.

By Mr. SCHNEIDER:

Q. Dr. Garonne—

The COURT: You might ask his name and his residence so that it will appear in the record.

Gaston Garonne—Direct

Q. Will you please state your name and residence?

A. Garonne, Gaston; Geneva, Switzerland.

Q. I show you a copy of an affidavit, paper No. 10 in Plaintiffs' Exhibit 1, the affidavit dated February 16, 1962. [95] Are you familiar with it?

A. Yes.

Q. This affidavit describes the use of the compound monochlorimipramine in the treatment of mental depression in 23 specific patients. Did you supervise or personally conduct the treatment of these patients?

A. I have supervised them.

Q. The affidavit states that you found the compound in suit, monochlorimipramine, to be an effective antidepressant and concludes that its therapeutic effect manifests itself faster than that of any other known thymolepticum.

A. Yes.

Q. Does this conclusion represent your present opinion?

A. Yes.

Q. Aside from the 23 patients mentioned in the affidavit, have you administered the compound in question to any other patients suffering from mental depression?

A. Yes.

Q. Approximately how many?

A. About 100.

Q. With what effect?

A. Similar effects.

Q. Would the results with these later patients cause

Gaston Garonne—Direct

[96] you to modify in any way the conclusions stated in your affidavit?

A. Yes.

Q. How?

A. In the following sense. I do presently consider that the monochlorimipramine has, with therapeutic doses, less side effects than the other compounds.

Q. In your affidavit, Dr. Garonne, you have emphasized the speed with which the compound takes effect. Will you explain why this is important?

A. This is important because the speed with which the effect takes hold reduces the period of latency.

The COURT: I don't understand what that means.

Mr. SCHNEIDER: We will ask him.

The WITNESS: During which period of latency the effects of the sickness still continue to manifest themselves.

By Mr. SCHNEIDER:

Q. And what do you mean by the period of latency, Dr. Garonne?

A. The period of latency is the period of time which is from the beginning of the treatment to the cure, to the clinical cure.

Q. Are there any dangers, Dr. Garonne, associated with [97] a prolonged period of latency?

A. Yes.

Q. And what are they?

A. The gravest danger is the suicide.

Q. How does the period of latency of monochlorimi-

Gaston Garonne—Direct

pramine compare with that of other drugs with which you are experienced?

A. More specifically, as far as imipramine itself is concerned, one can say that the period of latency with chlorimipramine is about half.

Q. Dr. Garonne, I show you Plaintiffs' Exhibit 11. Are you familiar with this compound?

A. Yes.

Q. Does it have anti-depressant properties?

A. Yes.

Q. How would you compare the speed of effect of monochlorimipramine with the compound shown in this exhibit?

A. The speed of effect of monochlorimipramine is about twice as fast as that of the compound in front of me.

Q. Would you compare the size of the dose required as between chlorimipramine and the compound shown in Plaintiffs' Exhibit 11?

A. The dosage of monochlorimipramine is about 75 [98] milligrams per day, while the dosage of imipramine is about 150 to 200 milligrams per day.

Q. Would you compare the severity of side effects as between chlorimipramine and imipramine?

A. With therapeutic doses there are much less side effects with monochlorimipramine than with imipramine.

Q. Are there patients to whom you would administer monochlorimipramine to whom you would not administer imipramine?

A. Yes.

Gaston Garonne—Cross

Q. And who are they?

A. Those are severely depressed patients where it is indispensable to obtain a very fast improvement for otherwise they would have to be hospitalized.

Q. I show you a copy of Defendant's Exhibit 4, Dr. Garonne, which is an article by Kuhn. Are you familiar with this article?

A. Yes.

Q. Is there anything in this article which would suggest that chlorimipramine might have anti-depressant qualities?

A. No.

Mr. SCHNEIDER: I believe that is all, Your Honor.

[99] The COURT: Any cross-examination?

Mr. ARMORE: Yes, Your Honor.

CROSS-EXAMINATION.

By Mr. ARMORE:

Q. Dr. Garonne, can you read English?

A. Relatively well.

Q. Is it a characteristic of different types of depression that they may suddenly disappear without any medication?

A. No.

The COURT: I wonder if the witness understood the question. Your question was whether some states of depression disappear without the use of medicine. Well, of course they do because the use of medicine for those states is rather recent.

Gaston Garonne—Cross

Mr. ARMORE: Yes, Your Honor, I believe that would be correct.

The COURT: I do think it is a matter of common knowledge that the use of medicine, except for tranquilizing drugs, is more or less recent in psychiatry, and yet people have been cured in the past without resort to medication. But I don't see that that is any reflection on any medicine.

Mr. ARMORE: Well, it is to this extent, Your [100] Honor: if these people were tested, who were presumably tested, would have at that stage of testing been relieved of their depression——

The COURT: That applies to any medicine because a doctor might test a medicine, say, for a cold and it might be successful, but the cold might have been cured by nature anyway. That is no reflection on the medicine.

Mr. ARMORE: However, that becomes——

The COURT: You may proceed. I didn't want to enter into a colloquy with counsel.

The INTERPRETER: The witness wishes to make a statement to that effect. The question was, specifically, that is it a characteristic, and the witness says it is not characteristic.

By Mr. ARMORE:

Q. However, does it happen in many instances that a patient who is depressed will actually come out of his depression without any medication whatsoever?

A. Not very often, or not often enough.

Q. Does a patient suffering from depression often

Gaston Garonne—Cross

seem to improve when he thinks he is being given a specific medication?

(Pause.)

[101] The COURT: I confess I share the witness' difficulty in quite understanding the question. Perhaps we will have the Reporter read it.

Mr. ARMORE: May I restate the question, Your Honor?

The COURT: Yes.

By Mr. ARMORE:

Q. Will a patient often recover from a depression when he is being given some pharmacologically inert substance, thinking he is being treated?

A. The answer is no.

Q. Are you familiar with the placebo effect of medication?

A. Yes.

Q. Is this a factor that can exist in connection with depressed patients?

A. Yes, but rarely.

Q. In the tests that were reported in your affidavit were the patients given other medication prior to the treatments with the monochlorine compound?

A. At the same time or prior to it?

Q. Prior.

A. Some of the patients.

Q. Were they given other anti-depressant therapy?

[102] A. Some of them, yes.

Q. Were they given other anti-depressant therapy

Gaston Garonne—Cross

simultaneously with taking the one chlorine compound?

A. No.

Q. For what period of time prior to the monochlorine therapy did you observe, personally observe these patients?

A. During the entire period of experimentation.

Q. Does that include a period of time prior to administering the drug?

A. Yes.

Q. How much of a period of time?

A. The time necessary to establish a diagnosis.

Q. How much time was that?

A. That could be one day, one week, or two weeks.

Q. Is it true that depressed patients go through different stages and at one stage they exhibit a non-depressed condition?

A. During the same period or during different periods?

Q. During their state of depression—I'm sorry—during the state of the disease.

A. No. During the present depressive stage, no.

Q. Will the present depressive stage frequently or often be followed by a non-depressed stage in such patients?

[103] A. In certain cases, yes, but after a very long period of depressive state.

Q. Did you use any controls in your tests that were reported in the affidavit?

A. No.

Gaston Garonne—Cross

Q. Is it reasonably possible that the results which are reported in the affidavit were the result of a placebo effect because a patient knew he was being treated?

A. No.

Q. How can you tell if you did not use controls?

A. Because it is characteristic of depressive states not to believe in the properties of the drug.

The COURT: Do I understand you to try to bring out, Mr. Armore, whether the medicine might not purely have had a psychological effect on the patient?

Mr. ARMORE: Yes, psychological.

The COURT: Well, even so it would have a good effect. To take a leaf out of another book, we hear a lot about lie detector tests. The lie detector tests themselves we don't consider reliable, but actually many a defendant in a criminal case has been led to make a confession when he was frightened that the lie detector would detect that he was lying even though actually it would not have done so. So it has its usefulness.

[104] So if a medicine convinces a person that it is going to cure him, maybe that medicine has a psychological value.

Mr. ARMORE: Except that it is well known in medical treatments that patients who exhibit a certain symptom, if given a sugar pill or a salt injection will recover and they don't have to take—and it doesn't prove that this particular drug had that effect.

The COURT: I see. Well, that is a matter of argument.

Gaston Garonne—Cross

By Mr. ARMORE:

Q. With respect to the tests reported in your affidavit, Dr. Garonne, I notice that out of the 23 tests which you report here, in nine cases over one week was required before the latency effect was achieved, is that correct?

The COURT: Well, the affidavit speaks for itself.

Mr. ARMORE: All right, strike that question.

The COURT: Suppose you withdraw the question. The affidavit speaks for itself.

Mr. ARMORE: Yes, I will.

Q. You have testified, Dr. Garonne, that you have also tested something like 100 additional patients—I withdraw that question at this point.

[105] In all of these cases that are reported in the affidavit, for how long were these patients observed after the few days of treatment was terminated?

A. For several months.

Q. Were they observed by you personally?

A. By my assistants and by myself. I have always been informed by them.

Q. Was this true of all these 23 cases?

A. Yes.

Q. You have testified that you have also treated 100 other patients with the one chlorine drug we are talking about.

A. Yes.

Q. Do you have a record of the conditions of those patients, the treatment and the results?

A. We do have clinical files on them.

Gaston Garonne—Cross

Q. But you don't have that record here in court, do you?

A. No, they have not been published.

Q. You have testified, I believe, that imipramine is a very effective anti-depressant compound, is that true?

A. Yes.

Q. You have testified that in connection with those 100 patients, I believe, that no serious toxic effects were [106] discovered, is that correct?

A. Yes.

Q. Do you have the clinical data here with you with respect to the results of those tests?

A. Are you speaking about the toxicity of them?

Q. The toxicity.

A. No.

Mr. ARMORE: I have here a volume, Medicinal Chemistry, which is a series of monographs, one of which monographs has been submitted by employees of the assignee of the present application, Geigy. I have photocopied the title page, the reverse of the title page, and some portions of the monograph relating to imipramine and its effectiveness as an anti-depressant drug. I would like to have this marked for identification as Defendant's Exhibit 6.

(Defendant's Exhibit No. 6 was marked for identification.)

By Mr. ARMORE:

Q. I ask the witness are those photocopies taken from that textbook?

Gaston Garonne—Cross

A. Yes.

Q. I refer you, Dr. Garonne, to page 88. Does the table and the material on that page indicate the results of [107] tests with more than 13,000 patients who had been administered imipramine?

The COURT: What page is this?

Mr. ARMORE: Page 88.

The COURT: Now finish your question.

By Mr. ARMORE:

Q. Does the data indicated on page 88 show that imipramine was highly effective as an anti-depressant in a substantial percentage; in fact, over 70 percent of the cases treated for depression?

The COURT: You are asking about some other medicine now?

Mr. ARMORE: I am referring to the non-chlorinated compound imipramine.

The COURT: I don't think this is proper cross-examination. I don't think that is within the scope of the direct examination.

Mr. ARMORE: The direct examination touched on imipramine.

The COURT: The direct examination consisted of a description of the efficacy of certain treatments on certain patients of the compound covered by the application in suit; so this is not within the scope of the direct examination.

[108] Mr. ARMORE: And also, Your Honor, the direct examination also touched on the results of treatment with this compound imipramine.

The COURT: I am going to exclude it, anyway, be-

Gaston Garonne—Cross

cause it makes no difference whether some other compound is equally good. The question is whether this compound does the work. For instance, there are probably dozens of cold medicines. That doesn't mean just because there are dozens of them, therefore they are of no value just because there isn't only one.

Mr. ARMORE: Your Honor, this compound is the compound of the patent that was just added to the record, Haefliger et al. This reference is concerned with the nonchlorinated compound which is the subject of the patent.

The COURT: But this is not proper cross-examination. I am going to exclude it.

Mr. ARMORE: Will Your Honor exclude this—

The COURT: I have not excluded the exhibit. I am excluding the cross-examination of this witness concerning this exhibit.

Mr. ARMORE: I would like to offer this exhibit into evidence as Defendant's Exhibit 5.

[109] The COURT: Let it be admitted.

(Defendant's Exhibit No. 6 for identification was received in evidence.)

The COURT: I would like to ask several questions of the witness.

How is this medicine administered? I mean by that is it in the form of a pill, in the form of an injection, or in the form of a liquid that is swallowed?

The WITNESS: In a pill.

The COURT: Doctor, you stated that in addition to the 23 patients that were treated with this medicine as described in the affidavit you also successfully

Pierre Deniker—Direct

treated 100 others. Now were there any others whom you attempted to treat with this medicine where the treatment was not successful?

The WITNESS: Yes.

The COURT: About how many?

The WITNESS: About 15 to 20 per cent.

The COURT: There is one more question. What side effects may be involved in the use of this medicine?

The WITNESS: With therapeutic doses the side effects could be dryness of the mouth, breaking out in sweat, difficulty of accommodation, sometimes slight cases of dizziness.

[110] The COURT: Is there any possibility of dangerous side effects?

The WITNESS: Not at therapeutic doses.

The COURT: Any redirect examination?

Mr. SCHNEIDER: No further questions.

The COURT: You may step down.

We will take our usual mid-afternoon recess at this time.

(Recess.)

Mr. SCHNEIDER: Your Honor, we have one further witness, Professor Deniker.

PIERRE DENIKER, called as a witness by Plaintiffs, having been duly sworn, was examined and testified through the Interpreter as follows:

Pierre Deniker—Direct

DIRECT EXAMINATION.

By Mr. SCHNEIDER:

Q. Will you please state your name, age, and occupation?

A. Pierre Deniker; 49 years old, Professor of Neuropsychiatry at the faculty of medicine in Paris, France.

The COURT: The University of Paris?

The WITNESS: University of Paris, France.

Q. What academic degrees do you hold, Professor Deniker?

[111] A. Doctor of medicine in 1945, and aggregation, which is a titularization, in 1961.

The COURT: I am sure that he would not be a professor at the University of Paris unless he was a gentleman of high attainments, because they have very high standards at the University of Paris, I know.

By Mr. SCHNEIDER:

Q. Professor Deniker, in your practice have you ever used—and I refer particularly, of course, to your practice in the treatment of psychotic and neurotic patients—have you ever used the compound monochlorimipramine?

A. With my research group we are in the process of making a systematic research about this particular compound.

Q. Approximately how many patients would you estimate have been treated with this compound so far?

Pierre Deniker—Direct

A. The systematic study of which I have spoken before comprises 150 patients.

Q. Were there other patients treated with the compound in addition to those involved in the systematic study?

A. Yes, the University Clinic of Paris uses this compound since four years ago.

Q. Can you estimate how many patients were treated in that way?

[112] A. I believe I can say several hundred.

Q. How would you rate the efficacy of this compound in the treatment of depressive states?

A. Its action is remarkable, very remarkable, in the treatment of depressive states, but not only in those.

Q. Are there any particular areas in which the compound is especially effective?

A. The research of which I have spoken concerns itself with fields in which other compounds are not effective. It concerns three types of patients, the severe depressions, the apathetic schizophrenia, and grave neurotics or a more exact term would be severe neurotics.

Q. Referring first to the use of the compound in the treatment of severe depression, prior to the use of this compound what was the usual technique applied?

A. I believe that all physicians, all treating physicians, are at the present time in agreement that the electroshock is the preferred type of treatment in urgent cases.

Q. Is it possible, Professor Deniker, to use mono-

Pierre Deniker—Direct

chloroimipramine as an alternative to electroshock in such cases?

A. This is precisely the object of our research, to show that an important percentage of patients can be treated [113] and cured with chloroimipramine, as well as with the electroshock.

Q. Is it desirable to avoid the use of electroshock if possible?

A. It is desirable.

Q. Why?

The COURT: Well, that is self-evident. Electric shock treatment is very extreme and, naturally, it would be used only when absolutely necessary. It is pretty much like avoiding a major operation if you can do so.

Mr. SCHNEIDER: Quite so.

By Mr. SCHNEIDER:

Q. Do you know of any other chemical drug, Professor Deniker, which could be used in place of electroshock?

A. It would be desirable that the question specifies in which type of case.

Q. I speak now of the use of electroshock in cases of severe depression where you have indicated that chloroimipramine can be used as an alternative in a substantial number of the cases.

A. As far as I am concerned, I know of no other chemical drug. If any are used, I think that the physicians are taking a grave risk of suicide.

Pierre Deniker—Direct

[114] Q. Are you familiar with the compound imipramine?

A. Yes.

Q. Do you consider it desirable to use this compound as an alternative to electroshock in the treatment of severe depression?

A. No.

Q. Professor Deniker, I show you Defendant's Exhibit 1-A.

The COURT: What is that?

Mr. SCHNEIDER: That is the Schindler patent, Your Honor.

By Mr. SCHNEIDER:

Q. I call your attention to the compound shown in example 2 of that patent. Are you familiar with this compound?

A. No.

Q. Has it ever, to your knowledge, been used as a psycho-pharmaceutical?

The COURT: Just a moment. The witness is a professor of psychiatry, he is not a chemist. Should you go into the chemical field with this witness?

Mr. SCHNEIDER: No; I just want to know, sir, whether he, of course, as a physician, is familiar with the various drugs that are used——

[115] The COURT: I understand, but don't show him a patent because the patent has a complicated formula. I presume he knows chemistry, but, after all, he is not an expert chemist.

Pierre Deniker—Direct

Mr. SCHNEIDER: I think our purpose has been served.

The COURT: I think you better reframe your question.

Mr. SCHNEIDER: He said he is not familiar with the compound, so we can let it go at that.

The COURT: I suppose you really have enough.

By Mr. SCHNEIDER:

Q. You stated, Professor Deniker, that there were three areas of mental illness in which this monochlor-imipramine was useful. The second, as I recall was apathetic schizophrenia.

The COURT: Don't give him all this prelude; just ask a question.

Q. Can you tell us what is meant by apathetic schizophrenia?

The COURT: We don't want to go into that. I presume it is form of schizophrenia. That is enough for this purpose.

[116] Mr. SCHNEIDER: The only think is there are some forms that this drug is useful in and others that it isn't, Your Honor.

The COURT: Very well. I think I will change my ruling.

What is meant by apathetic schizophrenia?

The WITNESS: Those schizophrenics where the symptoms are essentially in deficit.

Pierre Deniker—Direct

By Mr. SCHNEIDER:

Q. Can we explain their behavior?

A. This is easier. Those are patients which are essentially inert, retiring, and who refuse any activity and any participation in social life.

Q. Are anti-depressant drugs used in the treatment of this type of schizophrenia?

A. Yes.

Q. Is chlorimipramine used?

A. The chlorimipramine has given us interesting results in this particular field.

Q. Is imipramine used in this field?

A. All the anti-depressives could have been used for the treatment of these symptoms, but in conjunction with stimulants, because if we do not take this precaution of adding [117] stimulants there is a risk of having a cycle of agitation and a crisis of delusions.

Q. Professor Deniker, would you like to reconsider whether it is stimulants that are used with these anti-depressant drugs?

A. No, it is tranquilizers which are used at the same time with the anti-depressives.

Q. Will you compare the two drugs chlorimipramine and imipramine in their use in the treatment of this type of schizophrenia?

A. The new compound, namely, chlorimipramine, could have been administered in many cases without the help of any additional drugs and the quality of the results, that is, the quality of the social rehabilitation, has seemed to us distinctly superior to anything achieved with other anti-depressants.

Pierre Deniker—Direct

Q. Do the tranquilizers which you have referred to before have side effects?

The COURT: I don't think we want to go into that. That is a little far afield.

By Mr. SCHNEIDER:

Q. You also referred to the treatment of neurotics with chlorimipramine, Professor Deniker. Can you tell us why [118] chlorimipramine is especially useful in this field?

A. The cases of severe neurosis comprise the obsessive compulsion. These cases resist enormously psychotherapeutic as well as chemical therapeutic, and this is why we believe that the progress which has been made with chlorimipramine is significant.

Q. How does the dosage of chlorimipramine and imipramine compare?

A. The dosage of chlorimipramine is slightly less than half of that of the imipramine.

Q. Professor Deniker, I show you an article by Kuhn, Defendant's Exhibit 4. Are you familiar with this article?

A. I have read its translation into French at the time when it appeared.

Q. Do you find anything in this article which would suggest that chlorimipramine would have anti-depressant properties?

The COURT: I think this is cumulative. You have got that from the other witness. Anyway, it reads for itself.

Pierre Deniker—Cross

Mr. SCHNEIDER: Then I have no further questions, Your Honor.

The COURT: Very well. Any cross-examination?

Mr. ARMORE: Just a few questions, Your Honor.

[119] CROSS-EXAMINATION.

By Mr. ARMORE:

Q. Dr. Deniker, you stated that the——

The COURT: Just ask questions without summarizing his testimony.

Q. Has your research established that the chloro compound is a substitute for electroshock?

A. Yes.

Q. I understood you to testify that that was the purpose of the research but it had not yet been established.

The COURT: Don't tell him what you understood; ask him some questions. You can ask him has it been established, already established, or is that only an aim to be established in the future.

Q. Has it been definitively established that the chloro compound is a good substitute for electroshock, or is this simply the objective of your research?

A. We are going to publish in the next trimester the results of our studies showing that we have been able to replace electroshock with chlorimipramine treatments.

Q. Do you have any clinical data present in court showing actual tests that were made, the conditions of the tests, and the results?

Pierre Deniker—Cross

[120] A. No, I do not have it. The publication is just in the process of being prepared.

Q. Were controls used in any of the projects that you made?

A. The patients were their own control because these have been patients which we have followed for many years and which we consider, as it is called in French, follow-up studies.

Q. Did you use other groups of patients who were given non-pharmacologically active compounds simultaneously with these tests as a control?

A. We have definitely rejected the use of inert substances in cases of depressed patients for ethical and medical reasons.

Q. Did you simultaneously test groups of patients with other known anti-depressants in order to make parallel observations with the monochloro compound?

A. This has never been done simultaneously, but either previously or afterwards.

Q. What percentage of the patients that you treated with the one chlorine drug showed no response?

A. About 20 percent.

Q. Would you consider imipramine a very highly effective anti-depressant drug?

[121] A. Yes.

Mr. ARMORE: That is all, Your Honor. Thank you.

Mr. SCHNEIDER: No further questions.

The COURT: You may step down. Thank you.

Does the plaintiff rest?

Mr. SCHNEIDER: Yes, the plaintiff rests.

Mr. ARMORE: The defendant rests, Your Honor.

The COURT: I will be very glad to hear a brief sum-

Pierre Deniker—Cross

ming up in the morning if you would care to make an oral argument.

I think—and this I am addressing to all three counsel—I hope that you will be able to get this information for me by 10 o'clock tomorrow morning. I want to be sure whether under the present regulations of the Food and Drug Administration—I think that is the name of the organization—the mere fact that a drug is patented in this country, whether that is sufficient to permit the drug to be used or whether it still has to receive a permit after an investigation by the Food and Drug Administration. I am inclined to the view that it is the latter, but I want to be sure. I think that would be very important for me, Mr. Smith.

Mr. SMITH: Yes, Your Honor.

The COURT: I hope you can find this out between [122] now and 10 o'clock tomorrow morning.

* * * * *

[123] I will read over the testimony overnight. I think I would rather take the printed record with the joint appendix than the typewritten record.

I want to say that I was very much impressed by the testimony of Dr. Garonne and Professor Deniker.

(At 4:00 p.m. trial stood in recess, to reconvene 10:00 a.m., January 12, 1967.)

* * * * *

Plaintiffs' Closing Argument

[131] PLAINTIFFS' CLOSING ARGUMENT

Mr. SCHNEIDER: May it please the Court, the issue in this case is whether the new anti-depressant compound defined in claim 8 of the Schindler application would be obvious from the compounds shown in the prior art.

As Your Honor appreciates, the claimed compound contains one chlorine atom in the molecule. The prior art shows compounds with no chlorine atoms and compounds with twice as many chlorine atoms.

Whatever may be the structural similarities between the prior art compounds and the claimed compound, however, this is only one side of the story. Properties as well as chemical formulas must be considered on the question of obviousness.

The record shows that the prior art compound having two chlorine atoms is useless as an anti-depressant and that while the prior art compound having no chlorine can be used in the treatment of depression, the claimed compound acts twice as fast, is administered in half the dosage, has less side effects, and can be used in places where the prior art compound cannot be used, such as to replace electroshock treatment.

There is nothing at all in the art which would [132] suggest that these benefits could be obtained by introducing a limited amount of chlorine into the molecule. On the contrary, all the indications are, or were, that the presence of chlorine tended to suppress anti-depressant effect.

Thus we believe the compound is unobvious and it

Defendant's Closing Argument

is patentable and we ask the Court to make a finding and enter a judgment to that effect.

DEFENDANT'S CLOSING ARGUMENT

Mr. ARMORE: May it please the Court, as I have indicated with respect to the effect of the Food and Drug statute, the Food and Drug statute does not apply to compounds sold within one state; and as I have indicated, licenses are frequently granted to manufacturers within one state and consequently permission need not be granted or there need not be compliance with the Food and Drug regulations in order to sell the drug within a given state, as frequently happens.

The Compound under consideration by the Court contains one chlorine atom. That compound has been rejected in the Patent Office over a reference to Schindler et al, which discloses the same compound having two chlorine atoms.

This disclosure in Schindler et al is not a vast disclosure of a huge number of compounds because the Schindler et al patent, in example 2, specifically shows that compound, [133] names it and gives the structural formula, the two chlorine compound.

The COURT: Where is that?

Mr. ARMORE: The Schindler et al patent, and I refer the Court to Schindler et al, in column 2, at the bottom of column 2, example 2 specifically shows the structural formula of the two chloro compound and names it on the next page.

There are only two compounds in Schindler et al that are specifically disclosed by structural formula

Defendant's Closing Argument

and by name and there are only two examples, example 1 and example 2.

This is not a haphazard accidental disclosure. This is a clear, express, specific disclosure to the art.

Furthermore, Schindler et al says that the two chloro compound, as well as the other compounds, have an effect in the treatment of certain forms of mental disorders, without specifying the mental disorders. I refer the Court to column 1, starting at line 37, where the pharmacological properties of the Schindler et al compounds broadly are stated. Opposite line 40 in column 1 of the Schindler et al patent it indicates that Schindler et al compound is useful in the treatment of certain forms of mental disorders.

Now the secondary reference relied upon is the [134] Australian patent. The Australian patent discloses a class of compounds which correspond exactly to the class of compounds in Schindler et al and to the specific compound in Schindler et al. The Australian patent in fact indicates that these types of compounds may either be one halogen substituted or two halogen substituted.

Now the testimony indicates, and also the Australian patent shows, very significant pharmacological properties for the compounds disclosed there.

The COURT: I don't understand your point. You contend now that the formula contained in example 2 of the Schindler patent is the same as the compound of the application in suit. Isn't there a difference—

Mr. ARMORE: Only one difference, Your Honor.

Defendant's Closing Argument

The COURT: Only. Sometimes one little difference makes all the difference in the world.

Mr. ARMORE: That is the difference I am concentrating on. The only difference is it has an additional chlorine atom. So that the Schindler et al compound, the two chlorine compound in example 2, has the main nucleus of the compound substituted with two chlorine atoms. The claimed compound has the main nucleus substituted with one chlorine atom.

That is the difference between the claimed compound [135] and the Schindler et al example 2 compound.

The COURT: That is why you don't claim that as an anticipation, I presume.

Mr. ARMORE: Precisely, Your Honor.

The COURT: Now, then, on what do you base your contention that it was an obvious thing to eliminate one chlorine atom?

Mr. ARMORE: Simply on this: because the Australian patent shows a large class of compounds which may have one halogen, that is, one chlorine, or two chlorine atoms in the basic nucleus. The Australian patent shows a similar class of compounds which may have one halogen, that is, one chlorine atom, or two halogens, that is, two chlorine atoms.

Furthermore, the Australian patent also shows important pharmacological properties.

Furthermore, the testimony of the witness is that the Australian patent discloses a large number of compounds comprehended by that class.

The COURT: Thousands.

Mr. ARMORE: Thousands, millions.

Defendant's Closing Argument

Therefore, Your Honor, I submit the art knows that, viewing the Schindler et al compound shown to have certain undesignated efficacy for mental conditions, the art [136] knows from the Australian patent, showing thousands or millions of compounds which may be either one chlorine substituted or two chlorine substituted, it would suggest to the art that the two chlorine Schindler et al compound may be one chlorine substituted.

The COURT: I would be inclined to hold with you if the Australian patent, say, covered a dozen different compounds and it was just a question of trying each one of the dozen, experimenting and finding which one was best. I would say that would be a product of mechanical skill.

But when you have a disclosure of thousands of possibilities the selection of the particular possibility may involve the use of the inventive faculty, may it not?

Mr. ARMORE: Not in this case, Your Honor. As a matter of fact, in this case the fact that there are many, a vast number of possible compounds comprehended by the Australian patent is indicative of the fact that the art has taught that a large number of compounds may have either one chlorine atom or two chlorine atoms and yet have substantially the same properties.

The COURT: May I interrupt your train of thought with a question. Something was said yesterday about failure to disclose the use of this compound in the application. Well, [137] in going over all of this material last night I notice this statement in the application. It is one page 2 of the application and it states that the

Defendant's Closing Argument

substances covered by the application may be used for the treatment of certain forms of mental disorders, in particular, depressions.

Isn't that a disclosure of a purpose, for use in depressions?

Mr. ARMORE: Your Honor, the reason that contention was made is because this particular use is one of ten uses which have been disclosed. A variety of uses have been disclosed; but these uses have been disclosed not just for the claimed compound, these uses were disclosed for the class of compounds shown on page 1 of the application.

The COURT: I understand, but how can it be said that the applicant failed to disclose the use of this compound for depressions in the light of this statement?

Mr. ARMORE: Because in the preceding portions of the same paragraph among the uses——

The COURT: I have read the whole thing, naturally.

Mr. ARMORE: —among the uses are sedative. And the evidence in the record shows that a compound that is sedative has an entirely opposite effect——

The COURT: Mr. Armore, I am sure you would not [138] contend that because a dozen uses are disclosed of an invention that therefore no use is disclosed?

Mr. ARMORE: No, I don't contend that, Your Honor. What I do contend is that if mutually inconsistent uses are disclosed——

The COURT: Maybe his contention is wrong, but he does disclose it is useful for depressions.

Mr. ARMORE: A large number of compounds have a large number of properties. Two of those properties

Defendant's Closing Argument

are antithetical, actually mutually exclusive, sedative on the one hand and anti-depression is a stimulant——

The COURT: His argument may be entirely wrong, but he informs the public that my medicines covered by this application can be used in depressions. So I am not going to hold that he does not disclose use.

Mr. ARMORE: I really shouldn't argue that point because the Court of Appeals has already decided that there is a disclosure of anti-depressant.

The COURT: But this matter was repeated several times yesterday.

Mr. ARMORE: I don't believe I pressed that point, Your Honor.

The COURT: Well, maybe not.

[139] Mr. ARMORE: Because the Court of Appeals agreed with what you said.

The COURT: Maybe it was in the brief. I know I saw it somewhere.

In other words, you are not pressing that point.

Mr. ARMORE: I am not pressing that point, Your Honor.

The COURT: Fine.

Mr. ARMORE: However, I am pressing the point, and I would like to repeat this point just once if I can, the fact that the Australian patent covers a large number of compounds is even more indicative of the obviousness of the claimed compound in view of the fact that the Australian patent discloses a large class of compounds which have significant pharmacological properties which overlap the pharmacological properties disclosed in Schindler et al, and all of these compounds

Defendant's Closing Argument

are either one substituted or two substituted, can be one chlorine or two chlorine.

Hence, it would be obvious to one of ordinary skill in the art, viewing the two chloro compound of Schindler et al, that one of those chlorines can be omitted in view of what the Australian patent teaches.

The COURT: Very well.

Mr. ARMORE: That is one position that has been [140] taken.

The COURT: Now is there anything else?

Mr. ARMORE: Yes, Your Honor.

The second point I want to make is that we also rely upon the patent which was introduced into evidence yesterday, Haeffiger et al, which shows that the non-chlorinated compound is old in the art; that is, imipramine.

The COURT: In other words, you have on one side two atoms of chlorine, on the other side you have no chlorine at all, and the plaintiffs' compound is in between; is that it?

Mr. ARMORE: Well, that may be one view, Your Honor. Another view is simply comparing the plaintiffs' compound with the no chlorine compound. The plaintiffs' compound has one chlorine atom, the other compound has none.

The COURT: I always like to reduce contentions to simple terms. Perhaps I am a simple person. Is it your contention that since a compound with two chlorine atoms was known and a compound with no chlorine atoms was known, that it was no invention to produce a compound with only one?

Defendant's Closing Argument

Mr. ARMORE: That would be one point.

The COURT: What is your other point? State it simply. You are not arguing before a group of chemists. This is not the Board of Appeals of the Patent Office.

[141] Mr. ARMORE: My other point, Your Honor, is that since a compound with one chlorine atom is known—since a compound with one chlorine atom is claimed and it is shown to be an effective anti-depressant, and since a compound with no chlorine atoms was well known in the art as an antidepressant, there is no patentable distinction between the one chlorine—

The COURT: You are saying the same thing that I said, only in many more words.

Mr. ARMORE: Except that I am eliminating consideration of the two chlorine compound in this statement.

The COURT: Well, you can't eliminate it.

Mr. ARMORE: Considering a rejection based only on the non-chlorine compound.

The COURT: Very well. Now is there anything else?

Mr. ARMORE: Yes, Your Honor.

With respect to the evidence that has been adduced, I would like to make a few comments, if I may. The only evidence before the Court of comparative tests between the two chlorine compound and the one chlorine compound which is claimed, the dichlorine compound of example 2 of Schindler et al and the one chlorine compound, the only evidence before the Court of comparative tests is the testimony by Poldinger [142] which was submitted originally in the form of

Defendant's Closing Argument

an affidavit. That evidence was not submitted yesterday; it is previously submitted. In that evidence the tests consisted only—the evidence consisted only of testing ten patients with the dichloro compound.

The COURT: What evidence are you referring to?

Mr. ARMORE: The evidence by Dr. Poldinger which was submitted——

The COURT: Let's omit that. I am interested in the oral evidence introduced yesterday.

Dr. Garonne had 100 cases and Dr. Deniker has used this compound for four years in the Paris Hospital.

I agree with you that the Patent Office was right in its decision on the evidence presented to it because I think the evidence presented to the Patent Office was inadequate and if I had to decide this case on the evidence presented in the Patent Office I would uphold the Patent Office. Unfortunately or fortunately under the peculiar provisions of 35 U.S. Code 145 additional evidence is permitted. I don't know of any other administrative proceeding where a court can take additional evidence that was not before the administrative agency.

Mr. ARMORE: Your Honor, I submit that the testimony [143] by Dr. Garonne and Dr. Deniker have absolutely no probative significance, for this reason——

The COURT: Isn't that a rather extreme position?

Mr. ARMORE: It is a position that is substantiated by the prior decisions of this and other courts, for this reason: Dr. Garonne testified with respect to an affidavit showing tests on 23 patients. This related to an affidavit submitted in the Patent Office. With respect

Defendant's Closing Argument

to those tests he showed absolutely no use of controls whatsoever. Prior decisions of——

The COURT: I don't want you to say another word about his old affidavit because it is not sufficient. It is just a waste of time. The question is the sufficiency of the evidence introduced yesterday.

Mr. ARMORE: The evidence that was introduced yesterday with respect to the testing of 100 patients by Dr. Garonne, with respect to the testing of 150 patients by Dr. Deniker, I submit that in view of the absence of actual clinical experimental data this testimony generally amounts to nothing more than conclusions as to the efficacy of the monochloro compound.

I would like to refer Your Honor to a decision by this Court in the Commonwealth Engineering Company case, which [144] Your Honor has referred to, where similar types of testimony were presented and in which the Court said, "Such general conclusion is of no value as evidence." Now in that case, too, there were mere conclusions as to results. In both cases——

The COURT: These are not mere conclusions. The two together testified concerning several hundred specific cases.

You cannot say merely because the testimony was oral instead of by records of the individual experiments, that therefore it was conclusions. That does not make it conclusions.

I will tell you what would have been a conclusion, if he just said, I think this is a good medicine, then that would be a conclusion and I would ignore it.

But the testimony was that one doctor said he tried

Defendant's Closing Argument

it in 100 cases, the other said 150 cases, and that in all but 20 or 25 percent it was effective.

We know that no medicine of any kind is effective in 100 percent of the cases. You or I might have a bad cold and we might be given a prescription of a cold medicine and it might not help us. That does not mean that the medicine is not any good.

So that when the doctor reports successful results [145] in 80 percent of 250 cases, plus the fact that they have been using this in lieu of electric shock treatment for four years, that is not a mere conclusion.

I agree with you that mere conclusions are not enough.

Mr. ARMORE: May I suggest, Your Honor, that the statements that this drug was tested on several hundred patients and that the drug was found to be effective, without supporting evidence as to the conditions of the patients before tests, the conditions of the patients after tests, the dosage, the matter of observation, would indicate that the statements made by the witnesses in effect amount to mere conclusions.

The COURT: No, they are not mere conclusions. You might criticize their probative value, but we have to do some clear thinking. This is not a conclusion.

Mr. ARMORE: I submit, Your Honor, that they would have little probative value in the absence of actual clinical data supporting the conclusions which they have made.

The COURT: Well, it might have been better if they had brought clinical data from Europe with them, but hindsight is always better than foresight.

Defendant's Closing Argument

Mr. ARMORE: There are many instances, Your Honor, in which clinical data is presented and conclusions are [146] presented at the end of the clinical data, just as appears in the Garonne affidavit, where it is quite apparent that the conclusions which are drawn by highly skilled, highly reputable respected scientific authorities do not jibe with the actual clinical data preceding those conclusions.

I submit, therefore, that a mere conclusion that 100 patients were tested and the effect was found to be good is not a sufficient basis for drawing a conclusion for efficacy because it may be that if the actual data as to these various patients were examined they might not support the conclusions made by these witnesses.

Furthermore, may I also point out that these witnesses stated that imipramine, the non-chlorinated compound which is so closely related to the claimed compound which has one chlorine atom, these witnesses, especially the last witness, also said that imipramine is a very highly effective anti-depressant. Now that witness further stated that imipramine may not be quite as effective, but the fact of the matter is that they both exhibit the same identical properties; and as Your Honor knows and as the witnesses have indicated, it is known in the art that when you make a slight change in the molecular structure of a compound you would expect to retain the same basic properties but you also would expect [147] some changes to occur. And these changes that occur are not beyond the realm of expectation in view of the fact that both imipramine, the prior art non-chlorinated compound, is an effective

Closing Argument

anti-depressant and the claimed compound is an effective anti-depressant.

One more word, if I may say so.

The COURT: Surely.

Mr. ARMORE: In none of this testimony yesterday by either Dr. Garonne or Dr. Deniker was there any sufficient testimony as to the use of controls.

The use of controls is an important factor in valid scientific testing.

The COURT: Just what do you mean by controls?

Mr. ARMORE: By the use of controls I mean this, Your Honor: I mean that frequently a drug is administered, the patient knows he is getting the drug, the doctor knows he is getting what drug, and both the patient and the doctor see effective results. Scientific testing, however, requires that side by side with the patient who is given the drug which is being investigated there be another patient who is given no drug but exhibits the same symptoms, and there be another patient who is given a placebo, a pill which is pharmacologically inert, or that there be another patient [148] who is given a standard drug for that condition. For example, there is no evidence of side by side testing between the monochloro compound, which is shown to be an anti-depressant, or imipramine, the unchlorinated compound, which also has been conceded to be a very effective anti-depressant.

The COURT: Suppose another compound is equally good, does that detract from the patentability of this compound?

Mr. ARMORE: Yes, Your Honor, it does if the dif-

Plaintiffs' Rebuttal Argument

ference in structure is very small and both compounds are equally good, then the compound which is being claimed is unpatentable.

The COURT: For instance, there are probably hundreds of medicines for colds. Let's assume that they are all equally effective. They can all be patented if they comply with the patent law.

Mr. ARMORE: Only if the other compound is not obvious from the prior art compound.

The COURT: Yes.

Mr. ARMORE: If the other compound merely amounts to a small change in chemical structure, then it would be obvious, unless that compound exhibits some significantly different property.

[149] In this case the prior art compound I am talking about now is imipramine, the non-chlorinated compound. It has not been tested side by side with the claimed compound. No controls were used. Consequently, I submit that the present compound is unpatentable.

Thank you, Your Honor.

The COURT: Do you wish to say anything in reply?

Mr. SCHNEIDER: I just have a few points, Your Honor.

PLAINTIFFS' REBUTTAL ARGUMENT

Mr. SCHNEIDER: First of all, as to the disclosure of the Schindler patent, the two chlorine patent, Mr. Armore said that the patent discloses the use of that compound in the treatment of mental disorders broadly without specifically referring to depression. I merely

Plaintiffs' Rebuttal Argument

call attention to the fact that there are quite a number of other mental disorders than depression and some of these are treated by tranquilizers, which are quite different from the——

The COURT: I have to hear so much psychiatric testimony I don't want to hear any more if I can avoid it.

Mr. SCHNEIDER: Yes, sir.

The COURT: I know of course there are numerous mental disorders and depression is only one of them.

[150] Mr. SCHNEIDER: The second point was to point out that we have introduced evidence as to the natural results of combining the Australian patent and the Schindler et al patent, which is to put the tail of the Australian patent onto the body of the Schindler patent, and we have pointed out that all of those compounds are without activity so far as depression is concerned.

Finally, as to the testimony of Doctors Garonne and Deniker on the question of controls, I think that Dr. Deniker pointed out very well his view. He said from a practical and an ethical viewpoint he does not use controls. I think that the point is these people are sick and you have to treat them in the best way you can and it is not a laboratory animal.

I think that is all I have, sir.

The COURT: I mislaid my note yesterday which gave the name of this medicine in short. Would you write it out for me and hand it up to me now?

Mr. SCHNEIDER: Yes, sir.

Mr. ARMORE: Your Honor, may I make two points, please?

Plaintiffs' Rebuttal Argument

The COURT: Surely.

Mr. ARMORE: Your Honor raised the question if two [151] compounds exhibit similar properties, why one compound is not patentable over the other. There are a number of decisions by the Court of Customs and Patent Appeals which hold that closely related compounds are not patentable over prior art compounds unless they exhibit significantly different properties.

The COURT: Provided the step was obvious.

Mr. ARMORE: I am talking about closely related compounds in chemical structure.

The COURT: I mean provided the difference in structure was obvious.

Mr. ARMORE: If they are are closely related, Your Honor, the difference in structure is considered by a chemist to be obvious. If you just add one chlorine atom or you subtract one chlorine atom the difference in chemical structure to a chemist is obvious.

Does Your Honor want me to cite those decisions?

The COURT: No.

Mr. ARMORE: The last point, may I make the last point, on the matter of controls. I have two decisions I would like to bring to the Court's attention. One is a decision in *In Re Soli*, 50 CCPA 1289. I have the F. 2d citation, 317 F. 2d 941. In that case the Court specifically took [152] judicial notice of the use of controls in various experimental procedures.

Another decision, the last one, on controls, *In Re Irons*—

The COURT: What kind of a case was it? There are different types of controls and different kinds of cases. You can't always use controls.

Opinion of the Court

Mr. ARMORE: Your Honor, you can always use controls by applying a standard drug, you can always use controls by using a patient who has been given no drug, you can always use controls by giving a patient a placebo, a sugar pill or a salt injection.

The last case on controls, and this is my last point, is *In Re Irons*, 342 F. 2d 80, also 52 CCPA 938.

The COURT: I don't want the CCPA decisions. I have the F. 2d.

Mr. ARMORE: In this case the Court considered anti-arthritic drugs and the clear implications of this decision are two: One, that the number of patients treated must be statistically significant, there must be enough; secondly, that there must be some reasonable controls present in order to determine whether the tests have scientific validity.

Think you, Your Honor.

[153]

OPINION OF THE COURT

The COURT: This is an action against the Commissioner of Patents to authorize him to grant a patent on an application that he has rejected. The application was presented by Walter Schindler and another on December 4th, 1959, Serial No. 857,274.

This action was originally tried before another Judge of this Court and resulted in a judgment for the defendant. In reaching his decision the Trial Judge excluded from consideration certain evidence that had been introduced at the trial in behalf of the plaintiffs concerning tests on the compound involved in the application.

Opinion of the Court

The application relates to a medicine intended for use in mental diseases, specifically, conditions of depression.

On appeal taken by the plaintiffs the Court of Appeals disagreed with the Trial Judge and held that the evidence should have been considered. Accordingly, it remanded the case to this Court for the purpose of considering the evidence that was introduced at the trial and hear any further evidence that it saw fit to permit to be adduced and, finally, to make any findings of fact and conclusions of law.

First, there was evidence introduced in the form [154] of affidavits before the Patent Office as to certain tests with the compound in question, with a view to showing its efficacy. The Examiner held that the affidavits were insufficient to demonstrate the efficacy of the medicine. His rejection of the application was affirmed by the Board of Appeals.

If the record before this Court consisted solely of the record before the Patent Office this Court would be inclined to sustain the decision of the Patent Office. Additional evidence was introduced at the first trial of tests performed on patients, with a successful result. The Court has doubt whether that evidence, too, is sufficient to justify the conclusion of efficacy of the medicine, but the sufficiency vel non of that particular evidence need not be determined because at this hearing further evidence was introduced which the Court considers highly impressive.

The medicine involved in this case is chlorimipramine and is administered to patients suffering from

Opinion of the Court

depression for the purpose of counter-acting the depressive state.

Dr. Gaston Garonne, who is the head of the Psychiatry Department of the University of Geneva and a consultant of a cantonal hospital in mental matters, testified [155] that while in his original affidavit before the Patent Office he cited only 23 cases in which the medicine has been used, he has since that time used it in 100 additional cases with an efficient result. He testified that the medicine was not successful only in 15 or 20 percent of the cases. He also testified that there were less side effects than is expected or caused by other compounds at times and that such side effects as occasionally existed were not dangerous.

Dr. Pierre Deniker, Professor of Psychiatry at the University of Paris, testified that he and a research group working under him had administered the medicine involved in this application to 150 patients and that its action is remarkable in treating severe depressant states, apathetic schizophrenia, and severe neurotics. He testified that, in addition, at the hospital of the University of Paris the medicine has been regularly used for four years last past and several hundred patients were treated with it with success. He further stated that in only about 20 percent of the cases did the medicine fail to result in success. He further testified that this medicine can be used, in his opinion, in place of electric shock treatment and that it is gradually displacing electric shock treatment at the hospital of the University of Paris.

[156] The Court is convinced that this evidence is

Opinion of the Court

ample to demonstrate the efficacy of the compound involved in this application and the Court reaches this conclusion with due regard to its own observations in *Isenstead v. Watson*, 157 F. Supp. 7, and in *Commonwealth Engineering Co. v. Ladd*, 199 F. Supp. 51, affirmed 113 App. D.C. 53. These observations are to the effect that great care and scrutiny should be particularly taken in connection with applications for medical patents since the granting of such a patent gives a kind of official imprimatur to the public to the medicine in question on which as a moral matter some members of the public are likely to rely. To be sure, the Court of Customs and Patent Appeals, by a divided vote, took a different view of this particular point, the majority reaching the conclusion that the considerations to which this Court had occasion to refer should not be taken into account. This is one of several instances in which the District Court and the Court of Appeals, on the one hand, and the Court of Customs and Patent Appeals, on the other, differ on questions of patent law. *Application of Hartop*, 311 F. 2d 249.

As just stated, the Court fully took into account its expressions as to caution that should be used in granting medical patents but, and I repeat, here the evidence is ample [157] and strong to the effect that this medicine is efficacious, and the number of cases in which it has been successfully used is sufficiently large to justify such a conclusion.

It is urged, however, that the invention is obvious and therefore not patentable, since a similar compound is disclosed in a patent to Schindler, the same patentee

Opinion of the Court

as this applicant, issued on November 19th, 1957, 2,813,857. Among other things, that patent discloses a formula very similar to that of the compound here in question, the distinction being—and the only distinction—that the compound of the prior art contains two atoms of chlorine, whereas the compound of the application contains only one atom of chlorine. Offhand, the difference appears slight and the Patent Office was fully justified in reaching the conclusion that the invention was obvious in the absence of sufficient evidence that the compound of the application enabled the obtaining of superior results. The testimony of Dr. Garonne and Dr. Deniker, especially that of Dr. Deniker, was very strong in showing the superior efficacy of the applicant's compound. He testified that he knows of no other chemical that can be used as successfully for the same purpose.

It is not contended, of course, that this is the only medicine that can be used for conditions of depression. [158] The contention is that this is so far superior to other medicines for the purpose that it is being regularly used and even to the extent of supplanting electric shock treatment, which of course is a drastic treatment and if a treatment less drastic in nature can be substituted the result would be highly desirable.

There is a suggestion that the difference is one of degree. In one way all differences are differences of degree, but the difference in degree in this case is so large and so far reaching as to be equivalent to actually a new result. It has been held again and again that

Opinion of the Court

when a new result is obtained only a slight difference in structure is sufficient to justify patentability. Judge Learned Hand held that on a number of occasions in a couple of leading cases.

The Patent Office was not in a position to pass upon the evidence that was presented before this Court. It may well have been that the patent would have been allowed had all of this evidence been submitted to the Patent Office. The peculiarities of the procedure under 35 United States Code 145 are, however, that new and additional evidence may be submitted before the Court that was not available to the Patent Office. In this instance, of course, much of the evidence presented at this hearing could not have been [159] presented to the Patent Office because it did not exist at the time. Many of these tests and developments which I have already summarized have taken place since the action of the Patent Office.

While I reach the conclusion, therefore, that the invention was not obvious and has far-reaching efficacy, I am not reversing the decision of the Patent Office because I am acting solely on the basis of additional evidence. I am not disagreeing with the Patent Office on the record that was before it.

This Court, therefore, concludes that the plaintiffs are entitled to a patent on claim 8 of their application, which is the claim in suit, and judgment will be rendered accordingly.

You may submit proposed findings of fact and conclusions of law and a proposed judgement.

Opinion of the Court

The Court wishes to say it is indebted to all three counsel for a very able as well as interesting presentation of this unusual case.

(The trial stood concluded.)

REPORTER'S CERTIFICATE

Certified as the official transcript of proceedings.

GERALD NESBITT,
Official Reporter.

[1] UNITED STATES DISTRICT COURT FOR THE DISTRICT
OF COLUMBIA

Civil Action No. 3068-63

WALTER SCHINDLER and HENRI DIETRICH, PLAINTIFFS,

vs.

COMMISSIONER OF PATENTS, DEFENDANT.

Washington, D.C. February 8, 1967

The above cause came on for hearing before The
Honorable ALEXANDER HOLTZOFF, United States Dis-
trict Judge.

APPEARANCES:

CASPAR C. SCHNEIDER, JR., Esq., WILLIAM A. SMITH,
JR., Esq., for the Plaintiffs;

JACK E. ARMORE, Esq., Solicitor's Office, U.S. Patent
Office, for the Defendant.

Prepared for: Defendant, March 2, 1967.

DOYNE W. SPENCER.

Official Reporter

783-5700 Ext. 637

4806 U.S. Court House, Washington, D.C. 20001

Proceedings

[2] PROCEEDINGS

Mr. ARMORE: Your Honor, I represent the Defendant in Schindler vs. Commissioner of Patents, Civil Action No. 3068-63.

The Defendant indicates with respect to Proposed Findings submitted by the Plaintiffs that those findings are insufficient and that two additional findings should be made.

As your Honor may recall, this case was remanded by the Court of Appeals to the District Court.

The COURT: I recall it very well, because it was somewhat unusual.

Mr. ARMORE: Yes, your Honor. The Court of Appeals remanded the case for the reason——

The COURT: Will you pardon me just a moment. Let me read the Proposed Findings submitted by the Plaintiffs. I always believe that the prevailing party has the prior right to prepare findings.

I am going to strike out Conclusion of Law No. 5. That is argumentative.

Now Mr. Armore, I will look at your Proposed Findings.

Now, insofar as they go, do you have any objection to the Plaintiffs' Findings?

[3] Mr. ARMORE: No objection.

The COURT: But you want to add something else?

Mr. ARMORE: I would add two additional findings.

The COURT: Very well. Let me look at them. Where are your additional findings?

Mr. ARMORE: In the memorandum.

Proceedings

The COURT: You didn't submit findings in a separate document? I see.

Mr. ARMORE: No, your Honor. I combined them with the memorandum.

The COURT: Well, I am not going to find No. 1 and No. 2 because you practically are asking me to weaken my own decision.

Mr. ARMORE: Well, your Honor, the reason that we asked that these findings be made is because the mandate from the Court of Appeals indicated that findings had not been made on those two points before, and, consequently——

The COURT: I am practically treating this as a new trial. I am not going to make that finding because I don't think that the evidence justifies either of them.

Mr. ARMORE: May I make one point more, your Honor?

The COURT: Yes, sir.

Mr. ARMORE: Those findings are taken from the [4] opinion that the Court has rendered in this case.

The COURT: I have not said this. I did not say that the evidence would indicate that it was obvious. Did I say that in my opinion?

Mr. ARMORE: You did not say that, your Honor, but you did say this. May I say this? I am reading from the transcript of your opinion, your Honor: "If the record before this Court consisted solely of the record before the Patent Office, this Court would be inclined to sustain the decision of the Patent Office, which was that the"——

Proceedings

The COURT: That's an opinion. Opinions are not part of findings. I decline to make the finding.

Mr. ARMORE: Thank you.

The COURT: Now, as to No. 2, No. 2 is completely contrary to what I deemed the evidence justifies.

Mr. ARMORE: No. 2 refers only to the evidence in the first trial, and your Honor said in your opinion——

The COURT: I have treated all the evidence as one. I am not going to make those findings. I would be just stultifying my own decision if I did.

Mr. ARMORE: May I just make this last point. The next sentence after the one I just read is the sentence that corresponds to Finding 2.

[5] The COURT: I have declined to make the finding.

Mr. ARMORE: Thank you, your Honor.

The COURT: I am going to sign the findings as submitted by the plaintiffs with the exception of Conclusion of Law No. 5. I think that is superfluous.

Is the judgment in proper form, Mr. Armore?

Mr. ARMORE: I believe that it is, your Honor.

The COURT: Have you checked it?

Mr. ARMORE: I have checked it and I believe it is in proper form, your Honor.

The COURT: Very well. Thank you, gentlemen.

(Whereupon, the hearing was concluded.)

CERTIFICATE OF REPORTER

I, Doyne W. Spencer, hereby certify that I am a duly appointed, qualified and acting Official Court Reporter for the United States District Court for the District of Columbia; that the foregoing pages num-

Proceedings

bered 1 to 5, inclusive, contain a true and correct transcript of the proceedings had in the above-entitled cause on the date stated therein, and that said transcript is a true transcription of my stenotype notes taken therein.

DOYNE W. SPENCER,
Official Court Reporter.

Findings of Fact

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF
COLUMBIA

Civil Action No. 3068-63

WALTER SCHINDLER and HENRI DIETRICH, PLAINTIFFS,

v.

COMMISSIONER OF PATENTS, DEFENDANT.

FINDINGS OF FACT AND CONCLUSIONS OF LAW

1. This is an action brought under Section 145 of Title 35, United States Code, in which plaintiffs Walter Schindler and Henri Dietrich, as the applicants in patent application Serial No. 857,274, filed December 4, 1959, entitled "New Heterocyclic Compounds", seek a judgment from the Court authorizing the defendant, the Commissioner of Patents, to grant plaintiffs a patent.

2. Only claim 8 of said application Serial No. 857,274 is at issue.

3. Claim 8 is directed to a single specific compound, 3-chloro-5-(8-dimethylamino-propyl)-imino-dibenzyl, more conveniently referred to as chlorimipramine, which is useful as a medicine in the treatment of mental depression.

4. This action was originally tried before another Judge of this Court and resulted in a judgment for the defendant. In reaching his decision, the Trial Judge excluded from consideration certain evidence of anti-depressant properties that had been introduced on behalf of the plaintiffs.

Findings of Fact

5. On Appeal taken by the plaintiffs, the Court of Appeals disagreed with the Trial Judge and held that the evidence of anti-depressant properties should have been considered. Accordingly, it remanded the case to this Court to consider the evidence introduced at the first trial, hear such further evidence as in its discretion and at the request of the parties it might permit to be adduced, supplement the record with new findings of fact and conclusions of law, and return the enlarged record to the Court of Appeals.

6. Defendant relies upon the following prior art as rendering the claimed compound obvious and thus unpatentable:

(a) United States patent to Schindler et al., No. 2,813,857 which shows a compound having a molecular structure similar to that of the compound claimed but containing two atoms of chlorine, per molecule, where the claimed compound has only one. The prior art compound is indicated to be useful in treating "mental disorders", but mental depression is not specifically mentioned and, in fact, the compound is not useful for this purpose.

(b) Australian patent 215,335 which shows a very large class of compounds, some of which may contain only one chlorine atom per molecule. While this class of compounds is related to the compound claimed, it does not include that compound and requires a structural element, specifically a piperazine ring, different from any element of the claimed compound. The Australian compounds are not disclosed to be useful in treating depression.

Findings of Fact

(c) United States patent to Haefliger et al., No. 2,554,736 which discloses a compound like that claimed, but having no chlorine.

(d) An article by Kuhn in *Schweizerische Medizinische Wochenschrift*, Nr. 35/36, pp. 1135-1140 (1957) which indicates the non-chlorine-containing compound of patent No. 2,554,736 can be used to treat mental depression.

(e) *Medicinal Chemistry*, edited by George de Stevens, (1964) p. 88-89. This text, published after plaintiffs application was filed, also indicates that the non-chlorine-containing compound disclosed in patent No. 2,554,736 can be used to treat depressions.

(f) *The Chemistry of Organic Compounds*, Conant et al., Fourth Edition, pp. 407-411, 412-416, 438 and 448. This is simply a textbook of organic chemistry and has little connection with the issues here involved.

7. The compound of claim 8 is novel, in that it is not disclosed in any of the prior art relied upon.

8. The record, particularly the testimony of Dr. Gaston Garonne and Professor Pierre Deniker, shows that the compound in question has been used and is being used on a very substantial scale in the treatment of mental depression, with a very high degree of success.

9. Other compounds, such as that disclosed in patent No. 2,554,736 and the Kuhn article, have been used to treat depression, but the compound claimed is so far superior to those compounds that it can be used to

Conclusions of Law

supplant electro-shock treatment in severe depressions, a faculty not possessed by the prior art compounds.

10. The efficacy of the claimed compound as a medicine in treating depression, compared to that of the prior art compounds, is so large and far reaching as to amount to a new result.

11. The compound of claim 8 is not obvious from the prior art before the court.

CONCLUSIONS OF LAW

1. A chemical compound is patentable if it is new, useful and unobvious.

2. In considering the obviousness of a compound, its properties as well as its chemical formula must be considered.

3. Where a compound exhibits properties enabling a new result to be obtained, only a slight difference in structure is sufficient to justify patentability.

4. Plaintiffs are entitled to a patent containing claim 8 of application Serial No. 857,274.

ALEXANDER HOLTZOFF,
United States District Judge.

Date:—

Judgment

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF
COLUMBIA

Civil Action No. 3068-63

WALTER SCHINDLER and HENRI DIETRICH, PLAINTIFFS,

v.

COMMISSIONER OF PATENTS, DEFENDANT.

JUDGMENT

Pursuant to a mandate of the United States Court of Appeals for the District of Columbia Circuit dated December 26, 1966 that this Court should consider evidence of anti-depressant activity adduced at an earlier trial held February 16, 1965, together with such additional evidence as in its discretion and at the request of the parties it might permit to be adduced, a trial was held on January 11, 1967 at which trial additional evidence was introduced which included further evidence relating to the anti-depressant activity of the compound of claim 8.

Upon consideration of the entire record, the order previously filed by this Court on June 23, 1965, is set aside and it is, this 20th day of June, 1967.

ORDERED and ADJUDGED

That plaintiffs are entitled to receive a patent for the invention defined in claim 8 of their patent application Serial No. 857,274 and that defendant is authorized to issue a patent containing claim 8 of said application to

Judgment

plaintiffs, upon their compliance with the requirements of law.

As required by statute, costs will be assessed against plaintiffs.

ALEXANDER HOLTZOFF,
United States District Judge.

Notice of Appeal

UNITED STATES DISTRICT COURT FOR THE DISTRICT OF
COLUMBIA

Civil Action No. 3068-63

WALTER SCHINDLER and HENRI DIETRICH, PLAINTIFFS,

v.

COMMISSIONER OF PATENTS, DEFENDANT.

NOTICE OF APPEAL

Notice is hereby given that the Commissioner of Patents, defendant above named, hereby appeals to the United States Court of Appeals for the District of Columbia Circuit from the final Judgement entered in this action on June 20, 1967.

JOSEPH SCHIMMEL,
Solicitor, United States Patent Office,
Attorney for Defendant.

August 18, 1967

CERTIFICATE OF SERVICE

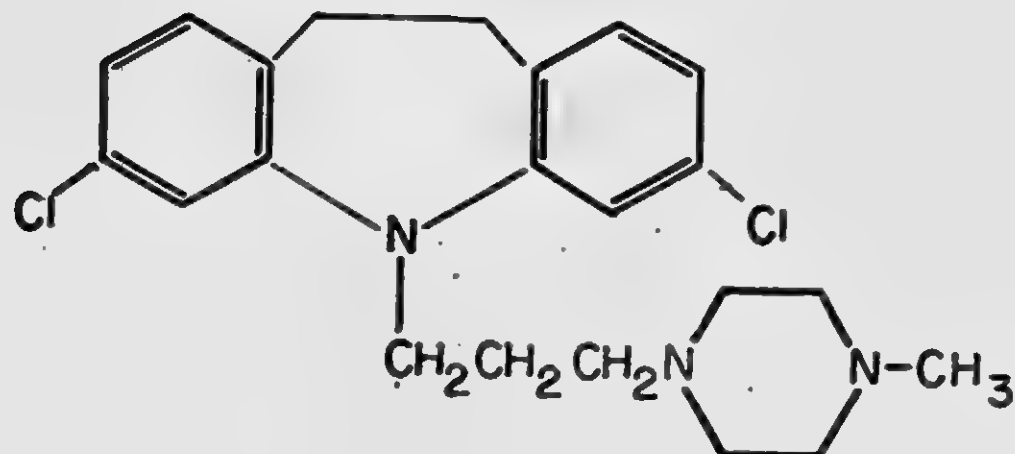
August —, 1967

I hereby certify that two copies of the foregoing NOTICE OF APPEAL were mailed today to the attorneys for the Plaintiffs, William A. Smith, Jr., Woodward Building, 15th and H Streets, N.W., Washington, D.C. 20005, Caspar C. Schneider, Jr., 30 Broad Street, New York, New York, and Karl F. Jorda, Ardsley, New York.

JOSEPH SCHIMMEL,
Solicitor.

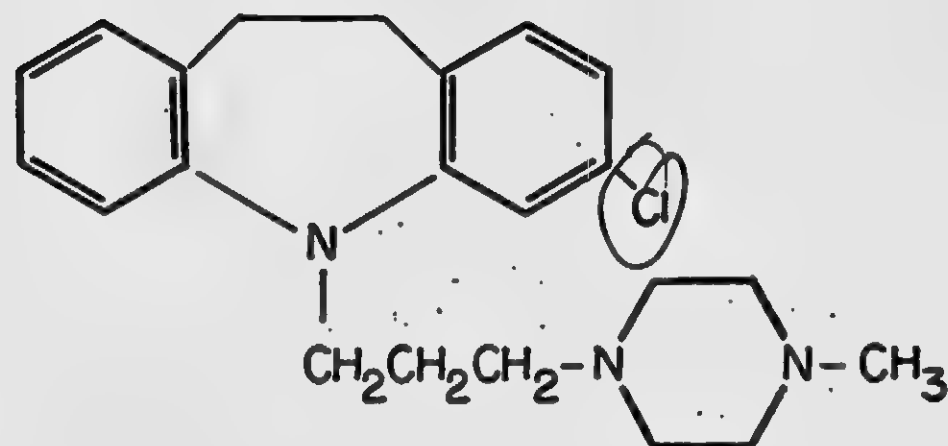


PLAINTIFFS' EXHIBIT 8



4-[3-(3,7-dichloro-10,11-dihydro-dibenzo[b,f]azepinyl-5)-propyl]-1-methyl piperazine.
Pharmacologically screened for activity on the central nervous system and found to be
completely inactive.

PLAINTIFFS' EXHIBIT 9



4-[3-(3-chloro-10,11-dihydro-dibenzo[b,f]azepinyl-5)-propyl]-1-methyl-piperazine.

Pharmacologically screened for activity on the central nervous system.

Slight activity as antagonist to apomorphine in the dog:

suppression of emesis at 2mg/kg s.c : 47%

Patented May 29, 1951

2,554,736

UNITED STATES PATENT OFFICE

2,554,736

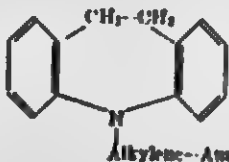
TERTIARY AMINOALKYL-IMINODIBENZYL

Franz Haefliger and Walter Schindler, Basel, Switzerland, assignors to J. R. Geigy A. G., Basel, Switzerland, a Swiss firm

No Drawing. Application June 26, 1950, Serial No. 170,472. In Switzerland July 22, 1949

4 Claims. (Cl. 240-239)

This invention relates to a new class of organic compounds and more particularly to basic derivatives of imino dibenzyl, to their salts and quaternary ammonium compounds and includes the manufacture thereof. The new compounds correspond to the general formula:



wherein alkylene and represents an alkylene chain of 2-6 carbon atoms and Am represents a low molecular dialkylamino radical (alkyl containing from 1-4 carbon atoms) or a N-piperidino-, N-morpholino-, or N-pyrrolidino radical in the μ -, γ -, or δ -position of the alkylene chain.

It has been found that these compounds possess valuable pharmacological properties. This, for instance, they produce anti-allergic effects and may be used for therapeutic purposes. The compounds in which Am is in the β -position of the alkylene chain are a preferred embodiment of the invention.

Imino dibenzyl is a known compound. It can be obtained by heating o,o'-diamino-dibenzyl chlorohydrate according to Thiele and Holzinger (Annalen, vol. 308, page 100 (1899)). Neither this basic compound nor any of its known derivatives have been of any therapeutic significance up to now.

The new compounds can be produced by two different, but co-related processes. Firstly imino dibenzyl can be reacted with a reactive ester of an alcohol of the general formula:



wherein alkylene and Am have the meaning given above, in the presence of acid binding agents. Sodium amide, lithium amide, potassium amide, sodium and potassium are suitable acid binding agents by means of which the imino dibenzyl can be advantageously converted into its alkali salt immediately before the reaction. The reaction should preferably be performed in an inert organic solvent such as benzene, toluene or xylene, by heating.

As reactive esters of an alcohol of the formula:



particularly the halide esters come into consideration such as dimethylamino ethyl chloride, diethylamino ethyl chloride, methylethylamino

ethyl chloride, piperidino ethyl chloride, pyrrolidino ethyl chloride, morpholino ethyl chloride, β -dimethylamino propyl chloride, β -dimethylamino isopropyl chloride, γ -dimethylamino propyl chloride, α -methyl- β -dimethylamino pentyl chloride, Di-n-propylamino ethyl chloride, methyl isopropylamino ethyl chloride, di-isobutylamino ethyl chloride, di-n-butylamino ethyl chloride or the corresponding bromides or iodides.

In the second process one mol of imino dibenzyl is reacted with one mol of a reactive mono- or di-ester of a glycol of the general formula:



wherein alkylene has the meaning given above, in the presence of an acid binding agent. Then, if a mono-ester has been used, the remaining hydroxyl group is converted into a reactive ester group. The reactive ester of N-hydroxyalkyl-imino dibenzyl obtained by either of these two variants of the second process is then reacted with a secondary amine of the general formula:



wherein Am has the meaning given above.

Particularly halide esters but also aryl sulphonic acid esters and mixed di-esters come into question as reactive esters of a glycol of the general formula:



Quaternary ammonium compounds can be obtained in the usual way from the tertiary amino alkyl-imino dibenzyls by the addition of halides or sulphates of aliphatic or araliphatic alcohols, e. g. methyl iodide, dimethyl sulphate, ethyl bromide or benzyl chloride. Such compounds can also be obtained, however, by the use of tertiary amines of the general formula:



wherein R represents an alkyl or aralkyl radical and Am has the meaning given above, in place of the secondary amines for the reaction with the reactive esters of N-hydroxy-alkyl-imino dibenzyls in the last step of the second process.

The tertiary bases form water soluble salts with inorganic or organic acids such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane disulphonic acid, acetic acid, citric acid, apple acid, succinic acid, tartaric acid, benzoic acid, phthalic acid.

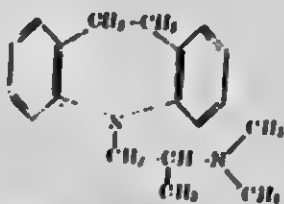
The following examples illustrate the inven-

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2,554,780

3

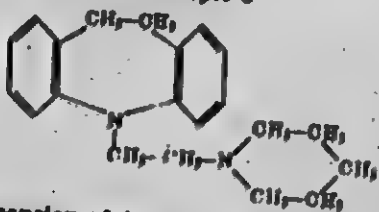
tion. Where not otherwise stated, parts are given by weight and the relationship of parts by weight to parts by volume is that of gram to cubic centimetres. Temperatures are given in degrees centigrade.



20 parts of imino dibenzyl are dissolved in 100 parts by volume of absolutely dry benzene. A suspension of 4 parts NaNH_2 in 50 parts by volume of abs. benzene are then added dropwise at 50-60° after which the mixture is boiled for an hour under reflux. 13 parts of β -dimethylamino isopropyl chloride are then added dropwise at 40-50° and the mixture is boiled for 10 hours under reflux. After cooling, the benzene solution is thoroughly washed with water, whereupon the basic constituents are extracted with dilute hydrochloric acid. The hydrochloric extract is then made alkaline and the separated base is extracted with ether. After drying, the solvent is evaporated and the residue is distilled in the high vacuum, whereby the N -(β -dimethylamino propyl)-imino dibenzyl resulting from a rearrangement in the side chain passes over at a temperature of 145-146° under 0.06 mm. pressure. The chlorohydrate with a melting point of 193-200° is obtained therefrom with alcoholic hydrochloric acid.

In an analogous manner, the following compounds are prepared: N -dimethylamino ethyl imino dibenzyl (B. P. 138-140° at 0.08 mm. pressure), chlorohydrate (M. P. 216-217°) from methanol/acetic ester; N -diethylamino ethyl imino dibenzyl (B. P. 150-152° at 0.15 mm. pressure), chlorohydrate (M. P. 192-193°) from methanol/acetic ester; N -(γ -dimethylamino propyl)-imino dibenzyl (B. P. 160° at 0.1 mm. pressure), chlorohydrate (M. P. 166-168°); N -(γ -dibutylamino propyl)-imino dibenzyl (B. P. 184° at 0.1 mm. pressure); N -(β -diethylamino propyl)-imino dibenzyl (B. P. 155-156° at 0.12 mm. pressure); N -morpholino ethyl imino dibenzyl, chlorohydrate (M. P. 220-222°).

Example 2



A suspension of 4 parts of sodium amide in 50 parts of abs. benzene are added dropwise at 40-50° to a solution of 20 parts imino dibenzyl in 10 parts by volume abs. benzene, after which the mixture is kept for 1 hour at 70-80°. It is then cooled to about 50°, 19 parts piperidino ethyl chloride in 40 parts by volume of abs. benzene are dropped in, after which the mixture is boiled for 10 hours under reflux. After cooling to about 5°, 30 parts by volume concentrated hydrochloric

4

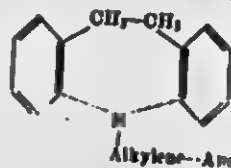
acid are added dropwise whereby the chlorohydrate of N -piperidino ethyl imino dibenzyl precipitates out. It is then filtered and recrystallized from abs. alcohol. It melts at 276-280° under decomposition.

The following compounds can be produced in analogous manner:

- 10 N -(β -dimethylamino-butyl)-imino dibenzyl.
 10 N -(di- n -butylamino ethyl)-imino dibenzyl.
 10 N -pyrrolidino ethyl imino dibenzyl.

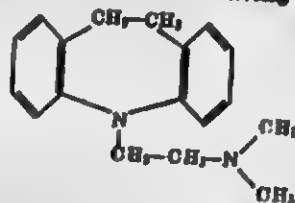
What we claim is:

1. A compound selected from the group consisting of a free base and its water soluble acid addition salts, said free base having the formula:

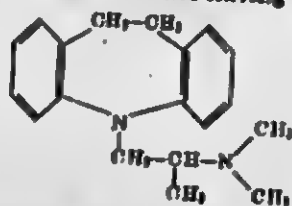


wherein alkylene represents an alkylene chain of 2-3 carbon atoms and Am represents a member selected from the group consisting of a low molecular dialkylamino radical, the N -piperidino-, N -morpholino-, and N -pyrrolidino radicals.

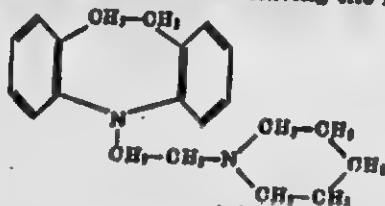
2. A compound selected from the group consisting of a free base and its water soluble acid addition salts, said free base having the formula:



3. A compound selected from the group consisting of a free base and its water soluble acid addition salts, said free base having the formula:



4. A compound selected from the group consisting of a free base and its water soluble acid addition salts, said free base having the formula:



FRANZ HAEFLIGER.
 WALTER SCHINDLER.

REFERENCES CITED

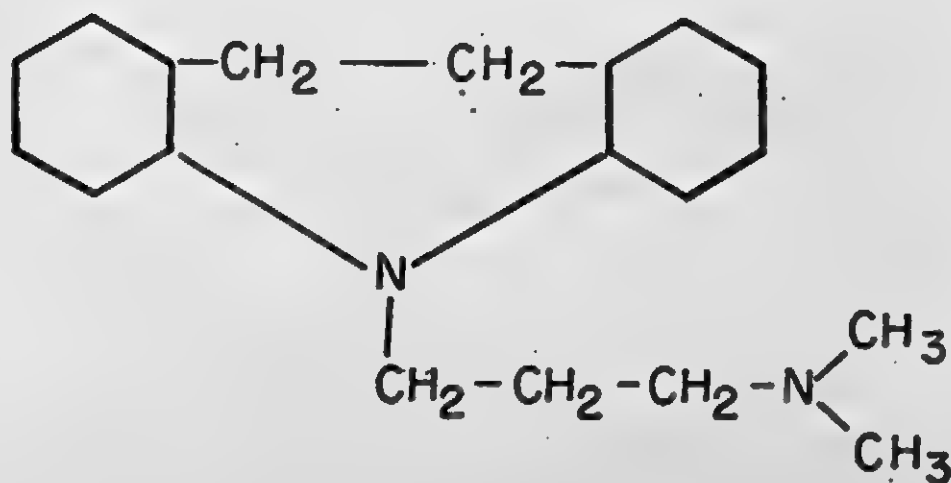
The following references are of record in the file of this patent:

FOREIGN PATENTS

Number	Country	Date
292,034	France	Mar. 27, 1943

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PLAINTIFFS' EXHIBIT 11

Patent 25547365-(γ - dimethylamino-propyl)-imino dibenzyl(imipramine)



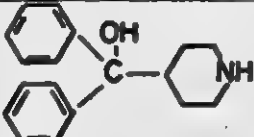
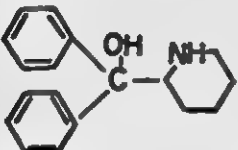
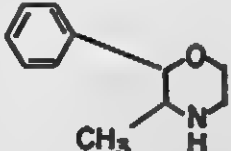
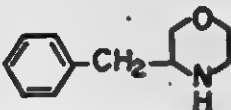
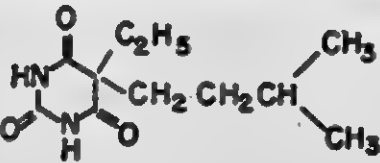
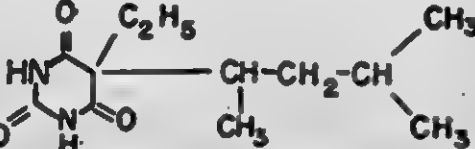
PLAINTIFFS' EXHIBIT 12

Pharmacological Comparison

<u>Activity</u>	<u>Dichlorimipramine</u>	<u>Imipramine</u>
<u>Anti cholinergic</u>	<u>92</u>	<u>24</u>
<u>Anti reserpine</u>	<u>225</u>	<u>5</u>
<u>Anti tetrabenazine</u>	<u>10 30</u>	<u>15</u>

PLAINTIFFS' EXHIBIT 13

Effect of Small Differences in Structure on Biological Activity of Chemical Compounds.

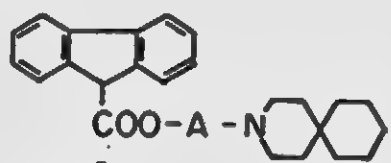
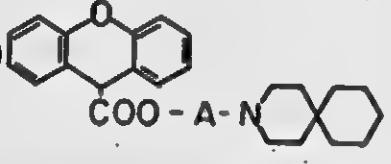
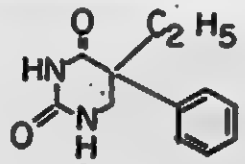
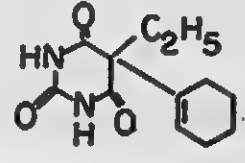
	Generic Name	Classification	Difference Between Compounds Activities		References
(a) 	Azacyclonol	Tranquilizer	Isomers	Antithesis	Cutting ⁽¹⁾ , p. 568
(b) 	Pipradol	Stimulant			Cutting, p. 581 U.S. Pat. 2,624,739
(c) 	Phenmetrazine	Stimulant Appetite Suppressant	Isomers	Antithesis	Cutting, p. 420
(d) 	—	CNS Depressant			U.S. Pat. 3,265,688
(e) 	Amobarbital	Sedative Hypnotic	Homologs	Antithesis	Cutting, p. 576 U.S. Pat. 1,514,573
(f) 	—	Antagonist to (e)			Cutting, p. 576

(1) W.C. Cutting, Handbook of Pharmacology (1962), Appleton-Century-Crofts, New York.

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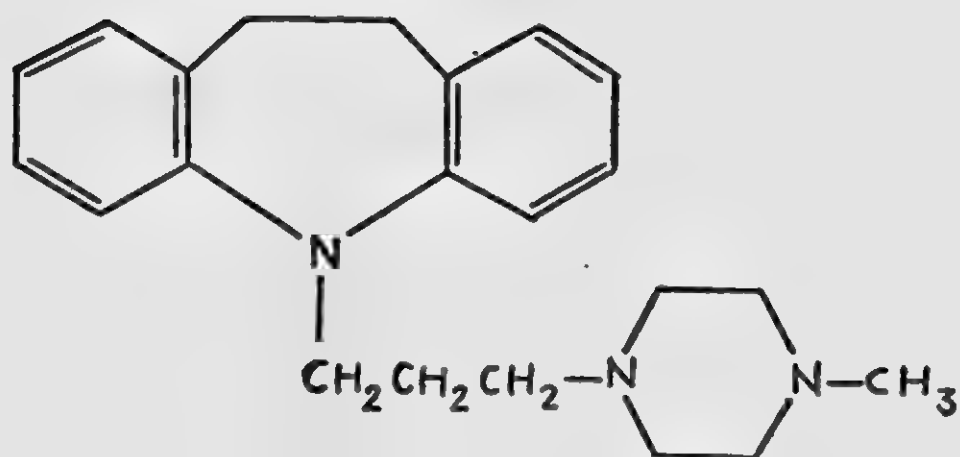
PLAINTIFFS' EXHIBIT 14

Effect of Small Differences in Structure on Biological Activity of Chemical Compounds

	Generic Name	Classification	Difference Between Compounds	Between Activities	References
(g) 	—	Hypotensive Antimorphine Stimulant	Bridge Between Phenyls	Utility	U.S. Pat. 3,265,701
(h) 	—	Anticholinerg. Antitremorine			U.S. Pat. 3,265,702
(i) 	Pheno-Barbital	Long acting Hypnotic	Nr. of Double Bonds	Duration of Effect	Cutting, p. 544 U.S. Pat. 1,025,872
(k) 	Cyclo-Barbital	Short acting Hypnotic			Cutting, p. 542

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4-[3-(10,11-dihydro-dibenz[b,f]azepinyl-5)-propyl]-1-methyl-piperazine
Pharmacologically screened for activity on the central nervous system:
Inactive.

DEFENDANT'S EXHIBIT 4

937

Schweizerische Medizinische Wochenschrift Nr. 33/36

1135

der Kantonalen Thurgauischen Heil- und Pflegeanstalt, Münsterlingen
Direktor: Dr. A. Zolliker

Über die Behandlung depressiver Zustände mit einem Iminodibenzylderivat (G 22355)

Von R. Kuhn

I. Die zur Zeit übliche Therapie depressiver Zustände und einige Probleme der Psychopharmakologie

Die verschiedenen Formen der Schwermut sind häufige, gefährliche und für den betroffenen Menschen nicht nur äußerst leidvolle, sondern oft auch folgenschwere Erkrankungen. Zu ihrer Behandlung stehen zwar in neuerer Zeit eine ganze Reihe von Methoden zur Verfügung, die ihre mehr oder weniger deutlichen, besonderen Indikationen haben (1). Es handelt sich aber dabei um weitgehend spezifische Therapien, die oft nicht recht befriedigende Ergebnisse zeitigen. Eigentlich entsprechen nur der experimentell auslöste epileptische Anfall bei endogenen und die Psychotherapie bei psychoreaktiven Depressionen einigermaßen den Anforderungen, welche an wirklich erfolgreiche therapeutische Maßnahmen gestellt werden müssen. Die Nachteile der Schockbehandlung sind allgemein bekannt. Psychoorganische Symptome treten besonders auf, wenn öfters Anfälle hervorgerufen werden müssen; recht selten ist die Wirkung nur anfänglich gut, und bei häufigen Rezidiven wird der Erfolg oft immer geringer. Zudem reagieren manche Kranke auf diese Behandlung überhaupt nicht. Die Psychotherapie auch vorwiegend reaktiver Depressionen kann äußerst schwierig und schwierig sein und gelingt auch nicht in allen Fällen. Allgemein-biologische, pathologisch-physiologische und psychopathologische Erfahrungen scheinen Versuche nahezu legen, depressive Zustände verschiedener Genese pharmakologisch zu beeinflussen. Jedoch hat sich bisher kein in diesem Sinne empfohlenes Medikament durchsetzen können. Vor allem Weckamine und ähnliche Stoffe beeinflussen zwar gewisse Formen der Depression gelegentlich etwas, meistens aber nur wenig oder gar nicht oder nur ganz vorübergehend, und sie führen leicht zur Sucht. Schlaf- und Beruhigungsmittel haben häufig überhaupt keine Wirkung, und wenn, dann am ehesten noch in der Form der alten Morphin-Opium-Kur. Ähnlich verhält es sich mit den Phenothiazin-derivaten und dem Reserpin. Eigentliche, überzeugende Erfolge sind von diesen selten zu sehen; wenn sie auch in einzelnen Fällen eine gewisse Erleichterung bringen, so können sie in andern wieder eine Verschlimmerung der vitalen Verstimmlung hervorrufen. So ist trotz dem qualvollen Zustand in vielen Fällen auch heute noch nichts anderes übrig als abzuwarten, bis die Depression von selbst abklingt.

Die pharmako-psychopathologische Forschung, die in erster Linie zur Abhilfe schaffen sollte, hat ganz allgemein mit großen, grundsätzlichen Schwierigkeiten zu kämpfen (2). Diese entstehen zum Teil schon aus der Vieldeutigkeit und der Unklarheit über das Wort „Psyche“ und die von diesem abgeleiteten Begriffe. Dann ist die diagnostische Erfassung depressiver Zustände gar nicht immer leicht, Irrtümer schleichen sich ein, und die Verwertung von Beobachtungsergebnissen ist schon deshalb nicht einfach. Es durchdringen sich zudem in zahlreichen Fällen endogene, organische und aktiv-psychogene Momente, was die Verhältnisse für pharmakologische Untersuchungen weiter kompliziert. Experimentell lassen sich solche Krankheiten nicht hervorrufen, und alle Prüfungen müssen am kranken Menschen selbst vorgenommen werden, auf dessen Angaben dann die Beurteilung einer Wirkung weitgehend angewiesen ist. Zudem sind die spontanen Verläufe sowie die Einflüsse des Milieus und der mitmenschlichen Beziehungen auf Schwere und Erscheinungsformen der Erkrankungen zu berücksichtigen. Am einfachsten ist es zweifellos, sedativ-hypnotische, die allgemeine Erregbarkeit herabsetzende Stoffe auf ihre Wirksamkeit zu prüfen und untereinander zu vergleichen. Schwieriger erscheint bereits die Abschätzung belebender und beräuschender Wirkungen, noch brauchbar das derartigen Beurteilungen zugrundeliegende Schema von lähmenden und erregenden Einflüssen auch sein mag,

es ist nicht ungefährlich, indem es die Forschung in vorausbestimmte Bahnen lenkt, die Aufmerksamkeit festlegt und manches übersieht, was vielleicht gerade wichtig wäre, um besondere, psychische Wirkungen von Medikamenten zu finden (3). Zudem lassen sich die großen Psychosen und vor allem die endogenen Gemüts- und Geisteskrankheiten nicht mittels eines so einfachen Schemas verstehen, das alles auf einen zwar biologisch sehr wichtigen, aber doch die Probleme viel zu sehr vereinfachenden Gegensatz zurückführt. Das Schema ist deshalb auch nur innerhalb sehr enger Grenzen geeignet, Untersuchungen über die Wirkungen von Arzneimitteln auf psychische Erkrankungen zu leiten. Die Publikationen über die psychopathologischen Auswirkungen der Phenothiazine und des Reserpins stellen vielleicht doch die sedativen und hypnotischen Wirkungen dieser Stoffe etwas stark in den Vordergrund (4). Wie kommt es aber, daß die Halluzinationen durch diese Medikamente ihre bedrohliche Nähe verlieren, in die Ferne rücken und die Wahnhaltungen den Kranken gleichgültiger lassen, fehlt doch dieser Effekt andern sedativ wirkenden Substanzen? Schon das zeigt wohl an, daß die beruhigende, lähmende Wirkung allein nicht als das entscheidende Prinzip für diese Einflüsse auf die Krankheit angesehen werden kann!

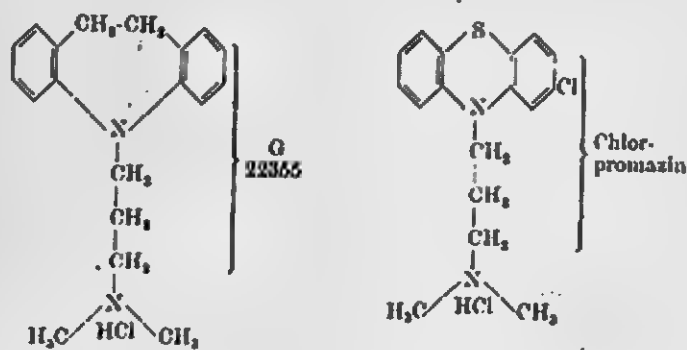
Klinisch-psychopharmakologische Untersuchungen von Iminodibenzylderivaten bei psychisch Kranken

Im Jahre 1950 hat uns die J. R. Geigy AG., Basel, ersucht, das Iminodibenzylderivat G 22150, einen Stoff mit histaminantagonistischen Eigenschaften, auf eine mögliche sedativ-hypnotische Wirkung zu untersuchen. Die erwarteten Einflüsse blieben in den zu jener Zeit verwendeten Dosen von 0,02–0,06 g meist aus; dagegen schien uns das Präparat eine auffallende Beruhigung Schizophrenen, die unter Erregungen, Wahnideen und Halluzinationen litten, hervorzubringen. Wir haben aber diese Wirkung gerade viel zu sehr lediglich unter dem einseitigen Gesichtspunkt der Beruhigung beurteilt und deshalb das besondere Interesse, welches solche Stoffe bieten, übersehen.

Zu Beginn des Jahres 1954 haben wir uns zusammen mit der J. R. Geigy AG. vorgenommen, die früher abgebrochenen Versuche fortzusetzen, und zwar im Hinblick auf die Fragestellung, ob die zu verwendenden Substanzen eine Wirkung auf Psychosen haben. Es waren die Erfahrungen der Basler Psychiatrischen Klinik mit Chlorpromazin bei Psychosen (5) und unsere früheren Beobachtungen, welche derartige Versuche nahelegten, sowie die von seiten der J. R. Geigy AG. mit G 22150 durchgeführten experimentellen Versuche hinsichtlich seiner Verwendung zur „hibernation artificielle“.

Seit mehr als 3 Jahren wurden nun ungefähr 500 Kranke der Heil- und Pflegeanstalt Münsterlingen mit verschiedenen Stoffen dieser chemischen Gruppe behandelt.

Die Ergebnisse all dieser Untersuchungen lassen sich in folgenden Sätzen zusammenfassen: Einige der untersuchten Iminodibenzyl-derivate sind als Medikamente geeignet. Es kommt ihnen eine Wirkung auf endogene Psychosen zu, die zum Teil ähnlich, zum Teil verschieden ist von derjenigen der Phenothiazinderivate. Ihre sedativ-hypnotische Wirkung scheint, nach den bisher geprüften Derivaten zu urteilen, geringer. In ihren vegetativen Wirkungen zeigen die Iminodibenzyl-derivate weitgehende Parallelen zu den homologen Phenothiazinverbindungen. Gefährliche Komplikationen wurden in allen unseren Versuchen nicht beobachtet. Wir haben bisher kein Derivat gefunden, welches das Chlorpromazin voll er-



¹ Wir danken der J. R. Geigy AG., Basel, für die sehr großen Versuchsmengen, die sie uns zur Verfügung stellte. Wir verwenden zur Zeit im Monat Iminodibenzyl-derivate in Mengen von ungefähr 20 000 Dragees zu 25 mg und fast 1000 Ampullen. Die Erfahrung zeigt, daß derartige Versuche nur in sehr großem Rahmen mit Erfolg durchgeführt werden können.

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setzen könnte, dagegen aber eine Verbindung, die eine dem Chlorpromazin fehlende, günstige Wirkung auf depressive Zustände hat. Es handelt sich um G 22355, das N-(γ -Dimethylaminopropyl)-iminodibenzylhydrochlorid.

II. Therapeutische Wirkungen und Nebenerscheinungen von G 22355

1. Einfluß auf depressive Symptome

Die bereits durch eine Beobachtung der Kranken von außen feststellbaren Symptome der depressiven Verstimmung werden unter G 22355 oft sehr deutlich besser. Die Mimik löst sich, sie gewinnt ihre Modulations- und Ausdrucksfähigkeit zurück. Die Kranken werden allgemein lebhafter, die depressive Flüsterstimme wird lauter, die Kranken erscheinen gesprächiger, das Jammern und Weinen hört auf. Wenn in der Depression eine unzufrieden-böigerische oder gereizte Stimmung bestanden hatte, macht diese einem freundlichen, zufriedenen und zugänglichen Wesen Platz. Hypochondrische und neurasthenische Klagen treten zurück oder verschwinden ganz. Kranke, die während der Depression am Morgen kaum aus dem Bett aufstehen wollten, verlassen dieses schon frühzeitig ganz von sich aus mit andern Patienten. Sie nehmen wieder Beziehungen mit andern Menschen auf, beginnen sich zu unterhalten, nehmen am allgemeinen Anstaltsleben teil, schreiben Briefe und bekümmern sich wieder um ihre familiären Angelegenheiten. Sie nehmen spontan eine Arbeit auf, verrichten dabei etwas, wie überhaupt die Langsamkeit aus ihrem Wesen weicht und einem normalen Lebenstempo Platz macht. Mit der Besserung werden die Kranken auf der Abteilung rasch beliebt, sie wirken in ihrer Stimmung und im ganzen Benehmen ausgeglichen. Mehrmals sind die Angehörigen in heller Begeisterung in der Sprechstunde des Arztes erschienen und haben erklärt, so gut sei der Kranke seit langer Zeit nie mehr gewesen.

Meistens, aber nicht immer, bemerken die Kranken die Veränderung auch selbst, geben sie zu, ja sie sind verständlicherweise selbst hoch erfreut darüber und sprechen von einer «Wunderkur». Die Gefühle der Schwere, der Müdigkeit und Schwäche, die Bedrücktheit, die innere Spannung, Verkrampfung oder Unruhe lösen sich. Die Kranken fühlen sich wieder frei, die Hemmung im Denken und Handeln schwindet, die Gedanken und die Aktivität kehren zurück. Eine traurige, gedrückte, verzweifelte oder angstvolle Stimmung schlägt um in eine neutral-unbeschwerte oder auch leicht heitere mit dem Gefühl des Gesundwerdens und steigender Kraft; krankhafte Schuldgefühle, Verarmungs- und Versündigungsideen verschwinden einfach oder verlieren ihre affektive Betonung, rücken in die Ferne, der Kranke steht ihnen gleichgültiger, distanzierter gegenüber. Ein heftigster Selbstmordantrieb ist gelegentlich plötzlich nicht mehr da! Wenn der Schlaf im Rahmen der depressiven Symptomatik gestört war, normalisiert er sich rasch, ohne zusätzliche Schlafmittel, auch in Fällen, die vorher gar keine Reaktion auf die üblichen Hypnotica erkennen ließen. «Schwere Träume», wie Depressive sie ab und zu zeigen, von Blut, Leichen, furchtbaren Unglücksfällen und grausamen Quälereien, die oft mit schrecklicher Angst einhergehen, erscheinen unter der Behandlung nicht mehr. Sehr rasch pflegen auch die morgendlichen Verstimmungen oder andere tageszeitliche Schwankungen des depressiven Zustandes nicht mehr aufzutreten. Wenn eine Appetitlosigkeit bestand, bessert sich dies ebenfalls, gelegentlich auch eine nur mit der Depression in Zusammenhang stehende Obstipation.

2. Eintritt und Dauer der Wirkung

Die Darreichung in Einzeldosen von G 22355 in Dosen von 25–75 mg hat bei verschiedenen Menschen und je nach Applikationsart verschiedene Wirkungen. Es wird entweder überhaupt nichts bemerkt, oder aber es treten Schlaftrigkeit, manifom-rauschartige Aufregungen sowie Erlebnisse auf, die unten als Nebenerscheinungen beschrieben sind. Die Veränderung wird je nach Art der Zuführung früher oder später, im allgemeinen jedoch rasch bemerkt und hält eine bis wenige Stunden an.

Die Wirkung von G 22355 auf depressive Zustände tritt bei bestimmten Fällen schlagartig nach einer Behandlung von 2–3 Tagen ein und ist dann gleich voll ausgeprägt, so daß man sagen muß, die

ganze Depression sei verschwunden. Oft erfolgt der plötzliche Umschlag der Stimmung erst nach etwa 1–4 Wochen, gelegentlich auch bloß nach und nach im Verlauf mehrerer Wochen.

Wird das Medikament wieder abgesetzt, bevor die Zeit vorüber ist, in welcher die Krankheit spontan abgelaufen wäre, tritt innerhalb von meist wenigen Tagen ein Rückfall ein, welcher das volle ursprüngliche Zustandsbild wieder herstellt. Erneute Verabreichung des Stoffes läßt in derselben Art, wie im Beginn der Behandlung, die Symptome wieder verschwinden. Ob das Medikament den Krankheitschub auch abkürzt, kann auf Grund unserer Untersuchungen nicht entschieden werden. Es bedarf wohl auch einer recht langen Erfahrung, um darüber etwas Zuverlässiges aussagen zu können. Bei sehr lange dauernder Erkrankung oder chronischen Fällen haben wir das Medikament dauernd weiter gegeben. In einzelnen Fällen wird es seit 2 Jahren verabreicht, ohne daß es seine Wirksamkeit verloren hätte. Eine gewisse minimale Dosierung ist aber zur Erhaltung des guten Zustandes notwendig, und es scheint, daß gelegentlich Schwankungen in der Intensität des Krankheitsprozesses oder andere Einflüsse eine vorübergehende Erhöhung der Dosierung notwendig machen.

3. Verabreichung und Dosierung

G 22355 kann in der Form von Dragées und Suppositorien oder durch intramuskuläre Injektion verabreicht werden (die ebenfalls mögliche intravenöse Injektion haben wir nicht verwendet). Allgemein kann gesagt werden, daß die Behandlung in Bezug auf Dosierung und Verteilung über den Tag ähnlich durchgeführt wird wie mit Chlorpromazin. Mit Vorteil werden eher öfters kleinere Dosen gegeben als einzelne größere. Bei leichteren Fällen, wie sie besonders auch in der ambulanten Praxis behandelt werden, gelingt es oft, mit peroraler Therapie allein eine hinreichende Wirkung zu erzielen. Wo dies nicht der Fall ist und besonders bei schweren Fällen, ist eine Behandlung mit Injektionen notwendig. Vor Beginn einer Injektionskur haben wir während 2–3 Tagen einzelne Dragées verabreicht, um eine eventuelle Ueberempfindlichkeit zu erkennen. Es wurde jedoch nie eine solche gefunden.

Die rein perorale Therapie wird mit 75–150, eventuell 200–250 mg pro Tag durchgeführt, falls nicht geringere Dosen bereits ausreichen. Bei der Injektionsbehandlung wird man 75–200 mg pro Tag verschreiben. (Es sind auch schon Versuche mit wesentlich größeren Dosen unternommen worden.) Nach 10–14 Tagen wird versucht, nach und nach eine Injektion zu 25 mg durch 2 Dragées zu je 25 mg zu ersetzen. Falls dabei Rückfälle auftreten, muß die Behandlung mit Injektionen wieder intensiviert und vielleicht, zum Teil wenigstens, in dieser Weise fortgesetzt werden. Wir haben das in einzelnen Fällen bis zu 1 Jahr durchgeführt. Eigenartig ist die Beobachtung, daß gelegentlich der Behandlungserfolg erst auftritt, wenn von Injektionen auf Tabletten übergegangen wurde; die Einleitung der Behandlung mit Injektionen war aber trotzdem notwendig. Es kann auch gelingen, mit Suppositorien auszukommen, die sich zu bewähren scheinen, mit denen die Erfahrungen aber noch gering sind.

4. Wirkungsbereich

Die geschilderten Erfahrungen stammen von 40 mit gutem Erfolg behandelten Fällen mit vorwiegend depressiven Zustandsbildern. Wieviele Kranke mit ähnlichen Störungen haben aber nicht oder nur ganz wenig reagiert? – Unsere Zahlen sind zu klein, um sichere Unterlagen für eine Statistik zu bieten. Zudem sind diese Probleme äußerst verwickelt. Sicher kann gesagt werden, daß nicht alle depressiven Zustände auf G 22355 ansprechen. Gelegentlich bleibt eine Wirkung überhaupt aus. Wir schätzen, mit allen gebotenen Vorbehalten, die bei einer üblichen klinischen Diagnostik versagenden Fälle auf etwa $\frac{1}{5}$ – $\frac{1}{4}$. Bei ungefähr $\frac{1}{4}$ – $\frac{1}{2}$ der Fälle ist der Erfolg derjenige einer Vollremission. Beim Rest der Kranken erzielt G 22355 zwar eine deutliche Besserung, die völlig genügen kann, um das spontane Abklingen der Krankheit abwarten zu können, aber keine völlige Remission. Wie bereits erwähnt, kann sich wohl das Verhalten ändern, der Kranke selbst aber glaubt nicht daran; dann wieder bleibt die Stimmungslage sehr labil und der Kranke getraut sich nicht, die Klinik zu verlassen; oder die Hemmung wird schwächer, verschwindet jedoch nicht ganz. In solchen

Man hat sich uns die Kombination mit Elektroschock in Narkose Relaxation und Sauerstoffbeatmung sehr bewährt. Meist genügen wenige Schocks, um die volle Remission zu erreichen, die nun mit einer Erhaltungsdosis von G 22355 von Dauer ist.

Wenn die Besserung nicht schlagartig, sondern nach und nach erfolgt, entstehen dieselben Gefahren wie beim spontanen Abklingen der Depression, wobei die Selbstgefährlichkeit mit schwindender Hemmung größer wird. Der Selbstmord eines depressiven Schizophrenen im Abort eines unserer Wachküle ist wahrscheinlich zustande gekommen. Bei ambulanter Behandlung ist diese Möglichkeit besonders zu berücksichtigen!

Wir haben G 22355 nicht nur bei vorwiegend depressiven Zuständen angewendet, sondern auch bei vielen Kranken, die neben depressiven auch depressive Symptome zeigten. Ferner haben wir Versuche bei vielen Fällen von reiner Schizophrenie, aber auch bei Schizophrenien und organischen Psychosen gemacht. Im ganzen wurden mehr als 300 Fälle behandelt. Wir glauben auf Grund aller unserer Erfahrungen gewisse Regeln zu erkennen, die einen Hinweis geben, wann der Stoff besonders gut wirkt. Dies ist in erster Linie der Fall bei typischen, endogenen Depressionen, auch solchen, die niemals im Klimakterium auftreten, sofern sie eine deutlich im Vordergrund stehende vitale Verstimmung zeigen. Je älter der Kranke ist, je länger die Depression dauerte, desto unsicherer und unvollkommener ist die Wirkung, wie dies ja oft auch für andere Behandlungen gilt. Wir haben aber bei fast der Hälfte unserer Fälle die Resultate erreicht, wo bereits andere Behandlungen gar keinen Erfolg nur einen ganz vorübergehenden oder sonst ungenügenden Erfolg gehabt hatten. Es finden sich Kranke, die auf Insulin- und Elektroschock-, auf Schlaf-, Chlorpromazin- und Reserpinkuren, auf Coffein, Weckamine und Meprobamat sowie auf lange Psychotherapie nicht oder nur unbefriedigend angesprochen hatten und nun auf G 22355 langandauernde Remissionen erfuhren, zum Teil endlich unter der Bedingung einer fortlaufenden Weiterbehandlung. Teilweises oder ganzes Versagen der Behandlung findet sich zunächst, wenn die Depression auf einer Epilepsie beruht. Zwar reagieren gelegentlich auch Verstimmungen und Dämmerzustände von Epileptikern auf das Medikament; es ist dies aber nicht die Regel. Von größerer praktischer Bedeutung ist die Einschränkung der Wirkung von G 22355 durch organische Hirnschädigungen. Schwierigkeiten bereiten besonders die mit den üblichen klinischen Methoden häufig nicht erfassbaren hirnatrophischen Prozesse, vor allem in deren Beginn. Gewisse Hinweise auf eine solche Krankheit können zwar bereits das klinische Bild und die Elektroencephalographie geben, entscheidend jedoch ist die Luftencephalographie. Ein hirnatrophischer Prozeß ist in höherem Lebensalter naturgemäß häufiger anzutreffen, und das öftere Versagen der Behandlung bei älteren Kranken ist nach unserer Erfahrung, sicher zum Teil wenigstens, auf übersehene derartige Komplikationen zurückzuführen. Immerhin muß gesagt werden, daß gelegentlich auch depressive Symptome von Organikern, auch wenn diese psychotisch entstanden sind, auf die Behandlung ansprechen, wodurch die Kranken sowohl wie deren Umgebung eine wesentliche Erleichterung verspüren. Ferner reagieren depressive Psychosen bei Hypertonie, wobei oft der erhöhte Blutdruck während der Dauer der Verabreichung etwas gemindert wird.

Schizoide oder schizophrene Züge in einem depressiven Zustand scheinen die Aussichten der Behandlung unsicherer zu machen. Damit werden neue, schwierige Probleme aufgeworfen, die mit der Wirkung von G 22355 bei schizophrenen Psychosen überhaupt in Zusammenhang stehen. Obwohl wir gegen 200 Schizophrenen zum Teil über lange Zeit behandelt haben, können wir heute darüber noch nichts Endgültiges aussagen. Sicher steht fest, daß das Medikament auch hier eine Wirkung hat, ja gelegentlich in Fällen, in denen Chlorpromazin und Reserpin versagen. Auch sehen wir akute Schübe der G 22355 bei Durchführung der Behandlung wie mit Chlorpromazin in gute Remission übergehen, ohne annehmen zu müssen, daß lediglich der spontane Verlauf beobachtet würde. Genau wie bei sogenannten Neuroplegia führt der Stoff in gewissen Fällen zu einer Distanzierung gegenüber den krankhaften Erlebnissen, auch rücken die Stimmen in die Ferne, und die affektive Beteiligung an den Wahnideen geht verloren. Auch kann sich die Zerfahrenheit etwas verringern. Es gibt aber andere Fälle, in denen die Be-

handlung lediglich eine die Schizophrenie begleitende, vitale Verstimmung behebt oder die Angst zum Verschwinden bringt, während die schizophrenen Symptome unverändert bestehen bleiben und vielleicht gar deutlicher hervortreten, wenn sie nicht mehr durch die Stimmungsanomalie verdeckt werden. Vor allem schizophrene Defekte kommen so unter Umständen besser zum Vorschein. Es kommt vor, daß die Kranken trotzdem vom Erfolg der Kur sehr erfreut sind, und sie können sogar entlassen werden und sich sozial viel angepaßter verhalten als vorher. Auch eine aus der Verstimmung entspringende Suizidalität kann verschwinden. Wir haben deutliche Besserungen ebenfalls bei schweren, chronischen Anstaltspatienten der verschiedensten Formen gesehen, auch bei Recidiven nach Leukotomie und in einigen völlig therapieresistenten Fällen. Freilich erschöpft sich hier die Wirkung oft in kürzerer oder längerer Zeit, und manche Fälle von Schizophrenie bleiben unbeeinflußt. Bei Stuporen scheint G 22355 recht unberechenbar. Man sieht, daß es den krankhaften Zustand gelegentlich löst; man sieht aber auch Stuporen während der Behandlung oder im Anschluß an deren Absetzen auftreten oder sich versteifen.

Die unregelmäßigen Erfolge des Medikaments bei Schizophrenie beruhen zum Teil auf dessen geringen oder fehlenden sedativ-hypnotischen Wirkungen. So ist sicher die akute schizophrene Erregung keine Indikation für die Anwendung von G 22355. Dasselbe gilt von manischen Zuständen. Hier gehen heute andere Medikamente vor, und erst wenn diese versagen oder wenn sie aus irgendwelchen Gründen (z. B. Allergie, Icterus) nicht mehr angewendet werden dürfen, ist ein Versuch gerechtfertigt. Ähnliches gilt von gelegentlichen Erregungszuständen chronischer Anstaltspatienten. Wo Jagen bei einer Schizophreniebehandlung der stark einschläfernde Effekt des Chlorpromazins unerwünscht ist, drängt sich eine kombinierte Behandlung mit G 22355 auf, oder umgekehrt, wo letzteres zu wenig beruhigt, kann eine Kombination mit Chlorpromazin oder im Rahmen unserer Versuche mit einem andern, stärker sedativ-hypnotisch wirkenden Iminodibenzyl-derivat eine ausgezeichnete Wirkung haben. Das stärker sedativ wirkende Medikament wird dann oft mit Vorteil auf die Nacht verabreicht. Im übrigen kommt gerade bei Schizophrenen dem G 22355 wahrscheinlich eine ähnliche «schocksparende» Wirkung zu wie dem Chlorpromazin, worauf uns Faust (Freiburg i. Br.) erstmals hingewiesen hat und was wir auch beobachten konnten (6).

Noch schwieriger ist die Frage zu beantworten, wie reaktive depressive Zustände auf G 22355 ansprechen. Wir haben verschiedene Fälle behandelt, wo Verstimmungen vorlagen, die einen gültigen realen Grund hatten. Bei einer alten Frau war es der Tod des geliebten Ehemannes, bei einer jungen Frau ein krimineller Abort unter sehr belastenden Umständen, bei einer Patientin im mittleren Lebensalter eine seit Jahren bestehende, schwere körperliche Behinderung durch Lähmungen infolge einer Poliomyelitis. Es war in diesen und andern Fällen eindrucklich, zu sehen, wie unter G 22355 die schwersten belastenden Situationen plötzlich einfach ihre Bedeutung weitgehend verloren, obschon sich an den tatsächlichen Verhältnissen gar nichts änderte. Heftigste, faktisch nur zu sehr begründete Schuldgefühle und Selbstanklagen können verschwinden, und das Leben geht plötzlich weiter, als ob nichts geschehen wäre. Wir haben beobachtet, daß die Gewissensbisse sich wieder zu regen begannen, sobald die Verabreichung des Medikaments ausgesetzt wurde. Zum Teil haben diese Fälle auch eine endogene Komponente aufgewiesen.

So einfach liegen die Verhältnisse nun aber nicht immer. Oft gewinnt man den Eindruck, daß gerade umgekehrt reale Gründe einer depressiven Verstimmung oder eine alte, in die Kindheit zurückreichende neurotische Entwicklung der Entfaltung einer Wirkung von G 22355 hemmend im Wege stehen oder wenigstens für die prompten Rückfälle nach Absetzen der Behandlung verantwortlich sind. Natürlich werden diese Probleme vor allem aktuell und dem Studium zugänglich bei den großen Psychotherapien. Im Verlaufe solcher Behandlungen kann das Medikament bei plötzlich auftretenden Verstimmungen oder Angstzuständen unter Umständen wertvolle Dienste leisten. Andererseits haben wir auch gesehen, wie seine Wirksamkeit sich änderte, je nachdem wie der Fortschritt in der Behandlung sich gestaltete. Nach einer jahrelang durchgeführten Psychotherapie, die nichts anderes als eine gewisse Er-

leichterung der schweren depressiven Symptome bei einer körperlichen Behinderung zustande brachte – trotz Lösung zahlreicher komplexhafter Erlebnisse und Erhellung der lebensgeschichtlichen Zusammenhänge bis ins Kindesalter –, gelang unter G 22355 die seit langem erhoffte Lösung der schweren vitalen Verstimmung in einer Woche weitgehend; dies ganz im Unterschied zu einer vorher während Monaten durchgeführten Chlorpromazinbehandlung, die nur eine leichte Besserung des Schlafes zustandegebracht hatte.

Diese Beobachtungen legen es nahe, die Frage zu prüfen, ob nicht Beziehungen bestehen zwischen G 22355 und andersartigen Stoffen, wie den Genußmitteln, die als «Sorgenbrecher» wirken, oder Medikamenten, wie den als «Tranquilizer» oder «Ataractica» bezeichneten Stoffen aus der Gruppe der Glycerinderivate, zu denen das Mephesisin und vor allem das von diesem abgeleitete Meprohamat gehören (7), sowie der Gruppe der Weckamine (8). Eine Beziehung läßt sich bei oberflächlicher Beurteilung leicht finden. Bei genauerer Betrachtung hingegen stellen sich rasch wesentliche Unterschiede heraus. Zunächst haben alle erwähnten Stoffe eben gerade keine eindeutig charakteristische Wirkung auf depressive Zustände! Dann wirken sie anscheinend entweder vor allem durch eine ausgesprochene sedativ-hypnotische Komponente oder umgekehrt durch einen deutlich hervortretenden erregend-berauschenden Effekt. Sie führen deshalb alle mehr oder weniger zu einer Sucht! Beide Wirkungen treten aber bei G 22355 zurück gegenüber einem ausgesprochen antidepressiven Effekt und einer Ähnlichkeit mit Chlorpromazin und Reserpin, die aber der Bezeichnung «Neuroplegicum» nicht voll entspricht.

Verhältnismäßig oft beschrieben ist die pharmakologische Beeinflussung von Angstphänomenen, und zwar sowohl im Sinne ihrer Erzeugung bei Vergiftungen als auch ihre therapeutische Verminderung. Weniger beachtet wurde die Wirkung pharmakologischer Substanzen auf Schuldphänomene. Es sind hier noch große Aufgaben, deren Bearbeitung von weittragendem Interesse ist, und zwar nicht nur für die Biologie und die Medizin, sondern vor allem auch für psychologische und philosophische Probleme.

5. Verträglichkeit

Im allgemeinen ist die Verträglichkeit gut. Bei peroralen Dosen in der Größe von 75–125 mg oder mit 75 mg als Injektion pro Tag besteht nach einiger Angewöhnung meist vollkommene Arbeitsfähigkeit sowohl auf körperlichem wie auf psychischem Gebiet. Wir haben Patienten, welche mit 5 Dragées zu 25 mg täglich auf dem Gutsbetrieb der Anstalt schwere landwirtschaftliche Arbeiten verrichten; eine als Patientin in der Anstalt weilende Krankenschwester hat während mehr als einem Jahr auf unserer Pflegeabteilung die volle Stelle einer Schwester versehen und dabei abwechselnd bald 75 mg G 22355 als Injektionen, verschiedentlich über mehrere Monate, oder 75–100 mg G 22355 per os bekommen, ohne in der Leistungsfähigkeit beeinträchtigt zu sein.

In einem andern Fall von endogener Depression, die den Kranken bisher immer gezwungen hatte, seine Arbeit gänzlich zu unterbrechen und für mehrere Wochen bis Monate in ein Sanatorium einzutreten, gelang es mit Dosen in der Größenordnung von 50–125 mg zunächst eine solche Besserung zu erzielen, daß er seine äußerst verantwortungsvolle, leitende Tätigkeit, die höchste intellektuelle Leistungen verlangt, fortsetzen konnte; ungefähr 4 Wochen nach Beginn der anfänglich mit zu geringen Dosen eingeleiteten Kur trat plötzlich eine volle Remission ein.

G 22355 kann ohne Schwierigkeiten kombiniert werden mit einem Phenothiazinderivat, mit Schlafmitteln – was freilich meist nicht notwendig ist –, mit den heute üblichen Behandlungsmethoden der gewöhnlichen Infektionskrankheiten und der Tuberkulose sowie mit Elektroschock.

6. Nebenwirkungen

Unsere Beobachtungen der Nebenwirkungen von G 22355 wurden an mehr als 300 meist klinisch beobachteten Fällen mit den verschiedensten, psychiatrischen Diagnosen gewonnen.

Aus den pharmakologischen Prüfungen, welche Domag in den Laboratorien der J. R. Geigy AG., Basel, durchgeführt hat, ergibt sich unter anderem eine dem Atropin ähnliche Wirkung auf verschiedene neurovegetative Regulationen. Die Toxizität der Verbindung, gemessen an den

mittleren Letaldosen bei Maus, Ratte und Kaninchen, entspricht ungefähr derjenigen des Chlorpromazins.

Kranke, welche sich einigermaßen selbst beobachten und Angaben machen können, beschreiben folgende Nebenwirkungen: Herzklopfen mit Pulsbeschleunigung, die meist anfallsweise auftreten, Schweißausbrüche, Trockenheit des Mundes, oft mit Durstempfindungen, und, besonders bei älteren Patienten, Akkommodationsstörungen und leichten Schwindel; seltener hören wir Druck im Kopf und allgemeinem Unwohlsein. Hier und da wird über Parästhesien geklagt.

Meist sind diese Nebenwirkungen geringer bei der Injektionsbehandlung als bei peroraler Verabreichung. Sie stellen im allgemeinen bloß eine gewisse Belästigung dar und gestatten meist die Fortsetzung der Behandlung in der optimalen Dosierung. Die Kranke gewöhnen sich innerhalb weniger Tage bis Wochen daran an das Medikament, daß sie überhaupt ohne irgendwelche Nebenwirkungen bleiben, oder sie spüren von Anfang an nicht Nebenwirkungen. Von besonderem Interesse ist jedoch das Auftreten einiger der erwähnten Symptome beim Zurückgehen der Dosierung, beim plötzlichen Absetzen und, wenn das Medikament in größeren Zeitabständen, etwa nur 1mal im Tag, genommen wird, vor dem Fällwerden der neuen Dosis. Die Störungen pflegen dann durch erneute Verabreichung zu verschwinden. Es scheint sich, gewöhnlich wenigstens, um Abstinenzerscheinungen zu handeln, die auch nach längerer Verabreichung und brücker Sistierung nur 2–3mal 24 Stunden dauern und dann von selbst verschwinden. Bedrohliche Symptome haben wir dabei nie beobachtet, und wir haben auch niemals irgendwelche Anzeichen einer Sucht beobachtet.

Bei Überdosierung oder unter normaler Dosierung bei gewissen anscheinend besonders disponierten Menschen (unter anderem bei akut schizophren Erkrankten) kann ein Erregungszustand auftreten. Es kann sich dabei um eine Aktivierung der Psychose mit Steigerung der Angst, der halluzinatorischen Tätigkeit und der Willkür handeln. Dann wieder beobachten wir einen akuten organischen Reaktionstyp oder eine vital-elementar anmutende Erregung, die keine besonderen Inhalte erkennen läßt, oder es entsteht ein maniformes oder rauschähnliches Bild. Letzteres freilich seltensten.

Es sind dies Phänomene, wie sie vor allem im Verlauf der Behandlung ja häufig beobachtet werden («turbulentes Stadium»), die auch bei Chlorpromazin vorkommen und sich durch andere unter Amiloribenzyl-ivate zum Teil besonders leicht analysieren lassen. Es ist heute bereits fest, daß die meisten bisher untersuchten derartigen Störungen keine oder höchstens eine geringe Wirkung bei Depressionen haben, allein schon verbietet, das Zustandekommen der Wirkung von G 22355 bloß in einer zur depressiven Hemmung in Antagonismus stehenden Erregung zu sehen.

Bei G 22355 treten die Erregungszustände zum Teil im Beginn der Kur auf und zwingen dann gelegentlich zu ihrem Absetzen, aber auch erst nach 1–2 Monaten oder noch später. Bei der Behandlung einer Depression stören die letzteren nicht, weil in dieser Zeit nur noch eine relativ geringe Erhaltungsdosis verabreicht wird, welche keine derartige Komplikation befürchten läßt.

Wie unter den andern Medikamenten kann die Erregung die Fortsetzung der Behandlung wieder verschwinden und einer Besserung der Psychose Platz machen, oder sie steigert sich so weit, daß die Behandlung unterbrochen werden muß. Im allgemeinen hat wir aus Vorsicht in diesen Fällen rasch mit der Behandlung aufgehört.

Schwerwiegende oder gar lebensbedrohende Komplikationen haben wir bei unseren mit G 22355 behandelten Fällen nie gesehen. Die allergischen Wirkungen scheinen verhältnismäßig gering sein. Beim Pflegepersonal wurde nie eine Überempfindlichkeit beobachtet. Bei den behandelten Kranken kam es einige Male zu flüchtigen Erythemen, gelegentlich in relativ geringer Ausmaße, z. B. schmetterlingsförmig über Nase und Wangen, in der Form verschieden ausgedehnter Flecken an den Extremitäten, bis zum fast generalisierten urticariellen Exanthem, die in einzelnen Fällen einen Abbruch der Behandlung notwendig machten. Bei einer Patientin, welche spontan zu Ekzemen neigte, ist während der Behandlung ein ekzematöser Schub aufgetreten, welcher bei Weiterführung der Medikation mit G 22355 wie frühere Schübe

* Wird später publiziert.

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scheit. Einzelne Kranke, die eine Überempfindlichkeit auf Chlorpromazin zeigten, konnten mit G 22355 ohne Zwischenfall behandelt werden. Personal, das auf Chlorpromazin sensibilisiert ist, reagiert nicht auf G 22355.

Ähnlich wie die Phenothiazinderivate führen diejenigen des Iminodibenzyls zu einer *Photorembilisation* für Sonnenbestrahlung. Mit Sonnenbädern ist deshalb während der Behandlung Vorsicht am Platz. Wir haben ferner eine Reihe von dafür geeigneten Patienten vor und nach verschieden langer Behandlung mit G 22355 mit andern Iminodibenzylderivaten durch den Ophthalmologen kontrollieren lassen². In keinem Fall konnten Anhaltspunkte für eine Schädigung irgendwelcher Art der Augen gefunden werden (9). Die Kranken haben auch nie über Störungen des Dämmerungssehens oder andere Abweichungen im Sehen geklagt außer über solche, welche auf die Beeinträchtigung der Akkommodation zurückzuführen waren.

Es stehen uns über 300 Blutstaten zur Verfügung, um die Frage des Einflusses von G 22355 auf das Blutbild zu beurteilen. (Wir fügen ferner über eine größere Zahl von Blutbildern, die bei Behandlungen mit andern Iminodibenzylderivaten gewonnen wurde und die, soweit wir bisher sehen können, ähnliche Resultate (weisen.) In 50 Fällen sind die Blutverhältnisse während Injektionskuren verfolgt worden. 36 Fälle konnten für eine Statistik verwendet werden. Die übrigen Fälle zeigen aber ähnliche Werte. Tabelle 1 gibt eine Übersicht über die Ergebnisse.

Tabelle 1

Durchschnittszahlen der Blutstaten von Injektionskuren mit G 22355

	Vor Beginn der Behandlung	36 Fälle			21 Fälle
		3.-5. Tag	5.-9. Tag	9.-14. Tag	12.-18. Tag
Hämoglobin %	91,2	—	—	88,9	88,3
Erythrocyten Mill.	4,7	—	—	4,6	4,6
Leukocyten	6208	6493	6358	6663	6252
Gran. %	82,2	83,4	81,8	82,7	81,2
Lk. %	4,6	4,9	5,4	4,9	5,3
Eosinoph. %	0,27	0,08	0,19	0,41	0,23
Thromb. %	2,6	3,4	3,6	4,0	3,3
Lymphocyten %	25,6	23,7	24,7	23,5	25,5
Monocyten %	4,3	4,2	4,2	4,3	4,0

Das Blutbild wird praktisch fast gar nicht beeinflusst, ausgenommen die Zahl der eosinophilen Leukocyten, die leicht ansteigt. Von 36 Fällen zeigten keine Reaktion der Eosinophilen. Der höchste Wert, der während der Kuren gezählt wurde, betrug 18% in einem Fall, welcher schon vor Beginn der Behandlung 14% eosinophile hatte. Dreimal haben wir 10% und einmal 11% gezählt. Patienten, die vor Beginn der Kur weniger als 5% Eosinophile hatten. Die Zahl der Leukocyten steigt in einzelnen Fällen auf 6000–12 000 und sinkt gelegentlich auch etwas; nur zweimal kam zu Zahlen unter 4000 (3900 und 3600).

Wir haben dann noch zwei weitere Gruppen von Patienten gebildet, bei denen das Blutbild nach länger dauernder Behandlung kontrolliert wurde: die erste Gruppe von 22 Fällen, die nach durchschnittlich 20 Wochen und die zweite Gruppe von 18 Fällen, die nach durchschnittlich 40 Wochen kontrolliert wurde. Auch hier ergeben sich keine wesentlichen Abweichungen. Die Zahl der Eosinophilen bleibt etwas erhöht mit 3,3% in der ersten Gruppe und 3,1% in der zweiten Gruppe. Hier finden wir zweimal 13%, einmal 10% und einmal 10% Eosinophile; die Leukocyten sind einmal auf 2900 gesunken.

Einmal ist während der Behandlung mit einem andern Iminodibenzyl-derivat ein typisches Pflaiffisches Drüsenfieber aufgetreten. Wir haben die Behandlung abgebrochen.

Der Blutdruck wird im Rahmen der von uns verwendeten Dosen geringgradig beeinflusst, meist sinkt er etwas, in einzelnen Fällen ist aber auch eine leichte Steigerung beobachtet worden. Bei Hypertonie haben wir Senkungen von 30–50 mm Hg beobachtet, während der Behandlung von vielen Monaten anhielten, sogleich wieder verschwanden, wenn das Medikament abgesetzt wurde.

Wir danken Herrn Kollegen Dr. Lüssi, Augenarzt in Frauenfeld, und ophthalmologischen Consiliarius des Thurgauischen Kantonsospitals in Winterthur, für die geduldige Untersuchung unserer Patienten und für die Erlaubnis, seine Berichte in dieser Arbeit zu verwenden.

Wo dieser Effekt eintritt, ist er meist von einer Besserung des psychischen Krankheitsbildes begleitet. Eine Neigung zu Kollapszuständen ist kaum zu beobachten. Wenn der Blutdruck, wie dies öfters bei Depressiven der Fall ist, auffallend niedrig ist, klagen die Kranken über besonders starken Schwindel, der auf eine zusätzliche Behandlung mit einem Kreislaufstimulans, wie Sympatol, gut anspricht.

Wir haben nur in 2 Fällen Thrombosen beobachtet und bisher nie eine Lungenembolie gesehen. Allerdings lassen wir die Kranken auch bei höherer Dosierung mindestens 2mal täglich einige Zeit außer Bett zubringen und, sobald sie es irgendwie ertragen können, aufstehen.

Symptome von seiten der Verdauungsorgane sind gering. Zwar kommt es bei vorherbestehender Appetitlosigkeit im allgemeinen zu einer Verbesserung der Nahrungsaufnahme, aber die bei Chlorpromazin immer wieder beobachtete Gewichtszunahme bleibt aus, falls nicht infolge der psychischen Erkrankung eine Inanition bestand. Einen sicher auf G 22355 zurückzuführenden Icterus haben wir bei 300 Fällen nie gesehen. Einmal ist ein solcher 6 Wochen nach Beendigung einer ganz kurzen Behandlung aufgetreten, ein anderes Mal zwar während der Behandlung, aber zur gleichen Zeit hatten wir zwei andere Fälle von Icterus auf der Abteilung bei Patienten, die keine entsprechenden Medikamente hatten. Nur einmal haben wir einen einzelnen, ganz leichten Icterus während der Behandlung gesehen, der spontan innert kurzer Zeit zurückging. Drei Patienten, die auf Chlorpromazin einen Icterus bekommen hatten, erhielten G 22355, ohne daß es erneut zu diesem Krankheitsbild gekommen wäre. Oft klagen vor allem Frauen, die bereits vor der Behandlung unter Verstopfung litten, darüber, daß diese während der Behandlung stärker geworden sei. Es kommt vor, daß eine eng mit der Depression zusammenhängende Verstopfung mit dem Eintritt der unter der Behandlung erreichten Besserung der übrigen depressiven Symptome verschwindet.

Auf dem Gebiet der Motorik fällt bei guter Beobachtung auf, daß die Mimik der Kranken unter der Behandlung etwas ärmer und steifer wird, falls der Gesichtsausdruck nicht bereits durch die Krankheit stark verändert war und die Besserung der Grundkrankheit dann auch eher eine Lösung im mimischen Bereich hervorruft. Außerdem kommt es etwa vor, daß ein sehr feinschlägiger Tremor auftritt; selten sieht man eigentliche parkinsonistische Zustandsbilder, die, wie bei Risperin und Chlorpromazin, auf eine entsprechende Behandlung reagieren. Am ehesten treten sie bei älteren Leuten auf, bei denen bereits ohne Medikamente eine gewisse Tendenz zu extrapyramidal-motorischen Dekompensationserscheinungen zu beobachten ist.

Bei unseren Versuchen mit Iminodibenzylderivaten ist uns immer wieder aufgefallen, daß Männer und Frauen auf chemisch gleiche Stoffe nicht ganz identisch zu reagieren scheinen. G 22355 wirkt bei Frauen anscheinend eher besser als bei Männern, und vielleicht neigen Männer dabei eher häufiger als Frauen zu Erregungszuständen.

Zusammenfassung. 1. Iminodibenzyl-derivate haben eine den Phenothiazinen und dem Risperin zum Teil ähnliche, zum Teil andersartige Wirkung auf Psychosen. Das N-(γ -Dimethylamino-propyl)-iminodibenzylhydrochlorid (G 22355 der J. R. Geigy AG, Basel), das ein anderes Ringsystem, aber dieselbe Seitenkette aufweist wie Chlorpromazin, hat sich aus einer Reihe untersuchter Substanzen als besonders wirksam und gut verträglich erwiesen.

2. G 22355 hat einen klar hervortretenden Einfluß auf die vitale depressive Verstimmung, besonders bei endogenen Depressionen. Auch psychoreaktive depressive Zustände zeigen oft eine deutliche Beeinflussung. Die Wirkung ist geringer und ein Erfolg unsicherer, sobald eine organische Hirnschädigung oder eine stärkere schizophrene Komponente vorliegt. Die Ursache für das Versagen der Behandlung in andern Fällen von typischen Depressionen ist nicht geklärt. In $\frac{3}{4}$ – $\frac{4}{5}$ der Fälle kann aber mit einem Erfolg gerechnet werden, der oft in einer vollständigen Remission besteht, oft in einer wesentlichen Besserung, die den Zustand erträglich macht. Auch schockresistente Fälle können reagieren. Anders bei Depressionen empfohlenen Medikamenten, wie Schlaf- und Beruhigungs-

mitteln, Chlorpromazin, Reserpin, Weckaminen und Meprobarat gegenüber erweist sich G 22355 als deutlich überlegen.

3. G 22355 wirkt auch bei Schizophrenen, aber nicht mit derselben Zuverlässigkeit wie bei Depressionen. Es beruht dies zum Teil sicher auf seiner geringen sedativ-hypnotischen Wirksamkeit. Es ist deshalb bei Erregungen und manischen Zustandsbildern nicht angezeigt und höchstens dann zu verwenden, wenn andere Methoden oder Stoffe versagen oder nicht angewendet werden können. Dagegen kann es bei nicht erregten Schizophrenen gut wirken.

4. Die Verträglichkeit ist im allgemeinen gut. Als Nebenwirkungen treten auf: Schweißausbrüche, Tachykardie, Trockenheit des Mundes, gelegentlich leichter Schwindel. Die Allergisierungstendenz ist gering. Das Blutbild wird kaum verändert; bei $\frac{2}{3}$ der Fälle wird eine leichte Steigerung der Zahl der eosinophilen Leukozyten beobachtet. Photosensibilisierung wurde mehrfach festgestellt. Gewissenhafte ophthalmologische Kontrolle einer Reihe unserer Patienten ergab nie einen Hinweis für eine Schädigung des Sehapparates. Die Akkommodationsfähigkeit wird durch eine akzessorische atropinartige Wirkungskomponente vorübergehend etwas beeinträchtigt. Unsere bisherigen Untersuchungen lassen keine endgültige Entscheidung über das Vorkommen von Icterus zu. Jedenfalls scheint diese Komplikation selten zu sein. Der Blutdruck wird nur sehr wenig modifiziert, am ehesten noch bei Hypertonie gesenkt, selten gesteigert.

Im Verlauf der Behandlung kann es zu Erregungszuständen kommen, die bei Weiterführung der Verabreichung wieder zurücktreten oder zum Abbruch der Behandlung zwingen.

5. Ein Stoff wie G 22355, der die depressive vitale Verstimmung beeinflusst, ist nicht nur praktisch-therapeutisch von großer Bedeutung, sondern auch theoretisch von hohem Interesse. Allgemein ergaben unsere Untersuchungen Hinweise auf die Möglichkeit, durch genaue Analyse der klinischen Beeinflussung scheinbar ähnlich wirkende Stoffe voneinander zu unterscheiden.

Summary. 1. Iminodibenzyl derivatives have an effect on psychoses that resembles those of phenothiazines and reserpine in some respects and differs from them in others. N-(γ -dimethylaminopropyl)-iminodibenzyl hydrochloride (G 22355, Messrs J. R. Geigy S.A., Basle) has a different ring system from chlorpromazine but the same side-chain; it proved to be especially effective and well tolerated in comparison with a number of other substances.

2. G 22355 has a distinct influence on depressive states, especially those of the endogenous type. The reactive type, too, is often distinctly influenced. The effect is smaller and success less assured in the presence of an organic lesion of the brain or a pronounced schizophrenic component. The reason for the failure of treatment in other cases of typical depression is not clear; however, success may be expected in three-quarters to four-fifths of cases. Complete remission may be achieved, or the condition may improve to a point where it becomes bearable. Even cases resistant to shock therapy may respond. G 22355 was found to be superior to other drugs commonly used in depressive states, such as hypnotics and sedatives, chlorpromazine, reserpine, amphetamines, and meprobarate.

3. G 22355 is also effective in schizophrenia but not as reliably as in depressions. This is certainly due in part to its low sedative and hypnotic activity. It is therefore not indicated in excitation and manic states and should be used in these conditions only when other methods or drugs have proved unsuccessful or are contraindicated. In schizophrenia without excitement, however, it may work well.

4. The drug is in general well tolerated. Side-effects consist of sweating, tachycardia, dryness of the mouth, and sometimes slight giddiness. Tendency to allergization is slight. The blood-picture is scarcely affected; in two-thirds of the cases a slight increase in eosinophil-count was observed. Photosensitization was observed in several instances. Thorough ophthalmological examination of a series of our patients showed no evidence of damage to the visual apparatus. An atropine-like action led to slight temporary impairment of the power of the eye to accommodate. Our observations

to date allow no conclusions to be drawn regarding the occurrence of jaundice; at all events, this complication seems to be rare. Blood-pressure is little affected; if anything, it is depressed in the presence of hypertension; it is seldom raised.

States of excitement may occur in the course of treatment. They either disappear spontaneously as treatment is continued, or compel its discontinuance.

5. A substance such as G 22355, which influences depressive states, is of great interest theoretically as well as practically. The results of our investigations indicate a possibility of "distinguishing" substances of ostensibly similar action by the careful comparison of their clinical effects.

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Travail de la Clinique universitaire de Psychiatrie, Bel-Air, Genève
Directeur: Prof. F. Morel †

Le vocabulaire psychiatrique de notre époque.

L'information qu'il communique

Par F. Morel †

«Es ist aber bey dem Gebrauch der Sprache auch dieses sonderlich zu betrachten, daß wir Zeichen nöthig haben, nicht nur unsere Meinung andern anzudeuten, sondern auch unsere Gedanken selbst zu helfen.»
Leibniz

En utilisant l'index des matières de plusieurs ouvrages contemporains en psychiatrie, j'ai relevé la liste des 250 mots à signification hautement psychiatrique les plus usuels. Cette évaluation sommaire donne une idée approximative de la terminologie actuelle en psychiatrie générale.

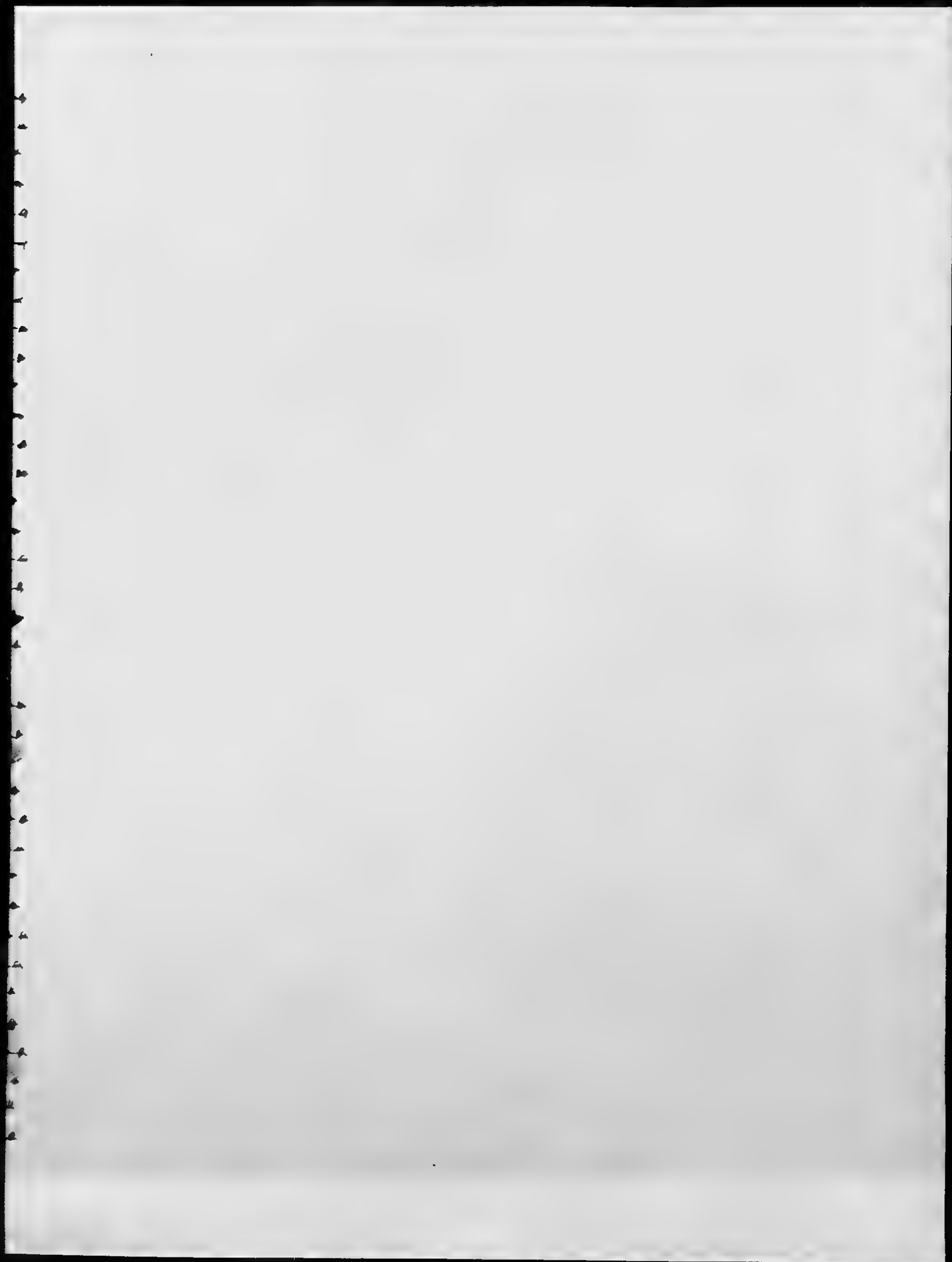
On ne trouve aucun nom d'objet dans celle-ci, à l'exception de très rares mots composés à partir d'un objet, comme *morphinisme*. L'ensemble est fait d'abstractions.

Morphologiquement ces mots abstraits présentent des catégories faciles à reconnaître par leur terminaison. 7 sur 10 de ces mots appartiennent à l'une des quatre catégories en *-ité*, *-ion*, *-isme*, *-ité*.

Les mots en *-ité* correspondent aux mots en *-et* et en *-ail* en allemand. Ils représentent approximativement le 5% des mots de la liste française, le 9% de la liste allemande. La distinction que fait apparaître l'allemand nous montre que cette catégorie en *-ité* contient d'une part des mots du langage courant et d'autre part des mots plus savants, des latinismes comme *puérilité*. Ces mots indiquent une propriété ou une qualité prépondérante de l'individu.

Les mots en *-ion*, plus nombreux en français qu'en allemand (20% et 10%), signifient des états pathologiques, observables par des tiers, mais aussi des états plus exclusivement subjectifs (*hallucination*, *obsession*).

Les mots en *-isme* sont environ 9% en français et en allemand. Ils indiquent une manière anormale de se comporter, le point de départ du mot étant soit la substance dont il est fait abus (*alco-*



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PSYCHOPHARMACOLOGICAL
AGENTS

EDITED BY

MAXWELL GORDON

*Smith Kline & French Laboratories
Philadelphia, Pennsylvania*

Volume I

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DEFENDANTS' EXHIBIT 6

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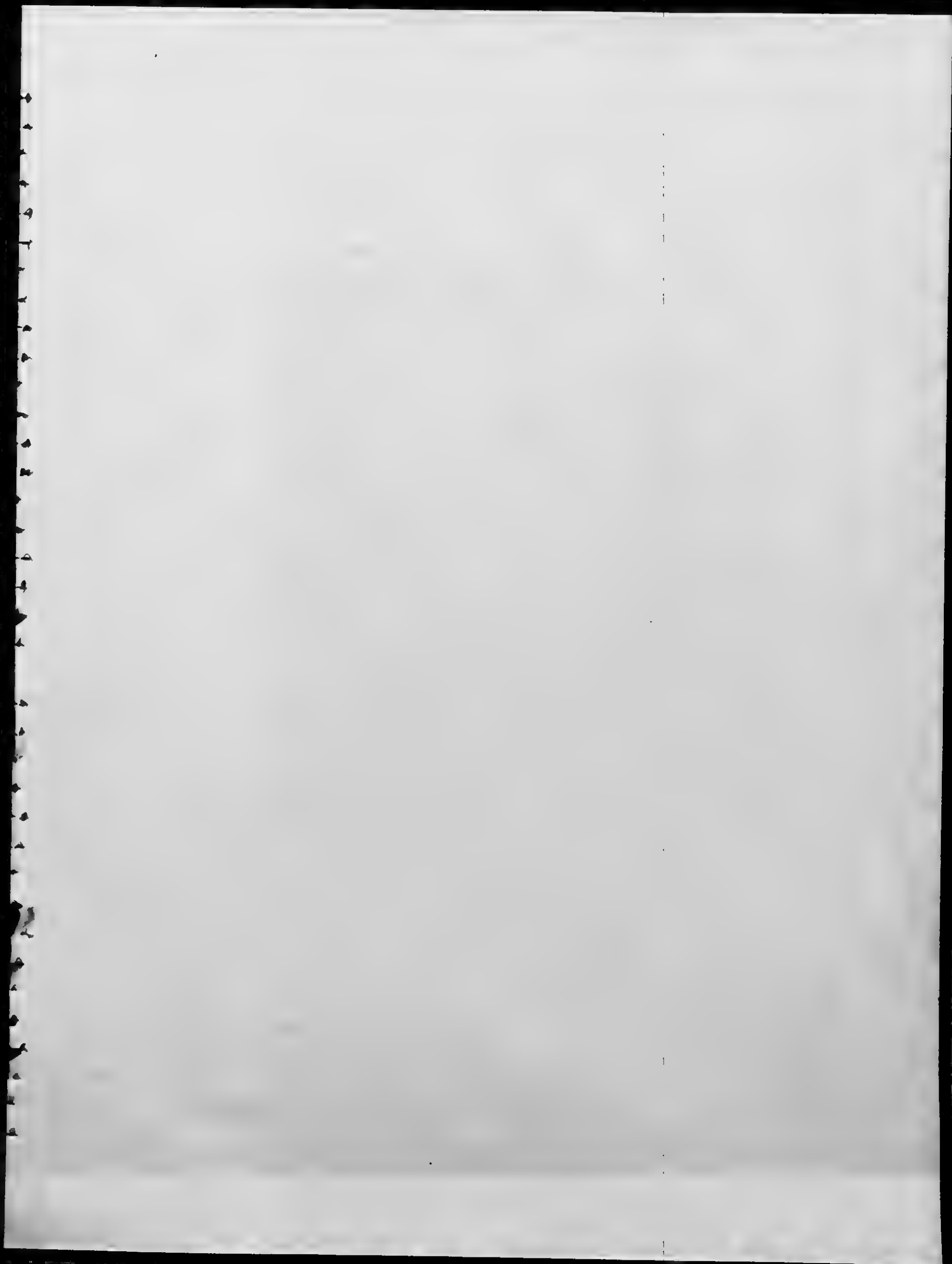
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PSYCHOPHARMACOLOGICAL
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[35] Iminodibenzyl and Related Compounds

FRANZ HÄFLIGER AND VERENA BURCKHARDT

*Pharmaceutical Research Department, F. R. Geigy
S.A., Basle, Switzerland*

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hydroxylation of the central seven-membered ring, and subsequent conjugation with glucuronic acid.

VI. SUMMARY OF CLINICAL APPLICATIONS

A. Imipramine

1. INDICATIONS AND CLINICAL RESULTS

Kuhn (1957) was the first to establish endogenous depressions (manic depressive disorders, involutional, recurrent, and climacteric melancholia) as the main indication for imipramine. Nearly all clinical investigators have corroborated his statement (Ayd, 1959; Azima, 1959; Freyhan, 1960; Lehmann *et al.*, 1958;

TABLE XVII

THERAPEUTIC RESPONSE TO IMIPRAMINE THERAPY

	All diagnostic categories	Endogenous depressions (including involutional)	Senile and presenile depressions	Reactive and neurotic depressions	Symptomatic depressions
Number of cases.....	13107	7807	324	3043	1933
Full remission.....	40%	46%	38%	34%	24%
Good improvement...	23%	24%	26%	24%	19%
Slight improvement...	14%	12%	16%	16%	18%
Negative.....	23%	18%	20%	26%	39%

Delay *et al.*, 1961; Dunlap, 1962). Other depressive states which respond favorably to imipramine therapy include reactive and neurotic depressions (Angst, 1961; Lehmann *et al.*, 1958; Kuhn, 1957) and symptomatic forms of depression. Depressive states are especially difficult to place into defined diagnostic categories.

An evaluation of 220 clinical papers (out of ca. 1000 published to date) is summarized in Table XVII; the division into diagnostic categories is inherently fraught with a certain degree of inaccuracy.

There are a number of single factors which can influence the therapeutic response to imipramine therapy in endogenous depressions: number of phases, course of the disease, age, sex. Most clinical investigators have related the psychopathological picture to the therapeutic result. In this connection the definition of "target symptoms" coined by Freyhan (1959) has gained importance. It is a fact that inhibited depressions respond best to imipramine therapy (e.g., Ayd, 1959; Coirault *et al.*, 1959; Fazio *et al.*, 1959; Hift and

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Kryspin-Exner, 1959; Kuhn, 1957; Delay *et al.*, 1961; Lehmann *et al.*, 1958). The opinions on the influence of imipramine on anxiety are divided.

2. SIDE EFFECTS AND CONTRAINDICATIONS

The most frequent side effects of imipramine are caused by its effect on the autonomic nervous system; they include dryness of the mouth, sweating, disturbance of accommodation, constipation, insomnia, and giddiness. In general, their nature is not severe; they usually fade away during 2-3 weeks or after reduction of dosage. Urinary retention has been observed in elderly patients (Harrer, 1961b).

Cardiovascular complications have been reported especially in elderly patients with damaged circulation (Mosbech, 1960; Rosen, 1960; Harel and Wijssenbeek, 1962; Kristiansen, 1961; Muller *et al.*, 1961). In these cases a cautious dosage and close observation with ECG is indicated.

Tremors and a Parkinson-like syndrome have been reported in very few cases (Colin, 1959; Lehmann *et al.*, 1958). Generalized convulsions have been observed in epileptics or patients with a pathologic EEG; caution is therefore indicated (Borenstein and Dabbah, 1959; Verdeaux and Mordret, 1960).

Allergic skin reactions are rarely seen; photosensitization is almost absent.

Isolated cases of icterus have been reported (Lund, 1962), likewise agranulocytosis (Bird, 1960; Blair 1960).

Combination of imipramine with MAO inhibitors may lead to complications; after treatment with MAO inhibitors an interval of 2-3 weeks should elapse before imipramine therapy is started (Harrer, 1961a).

Imipramine is relatively nontoxic; attempted suicides with 30 mg/kg have been unsuccessful. Especially in ambulatory treatment, however, the risk of suicide has to be considered. Like other antidepressants, imipramine may remove the psychomotor inhibition before the change in mood is obtained, thereby increasing the danger of suicide.

3. LABORATORY FINDINGS

Urinary status remains unchanged under imipramine therapy.

Leucocytosis and leucopenia have been reported (Leyberg and Denmark, 1959), also eosinophilia (Kuhn, 1957). No other permanent changes in blood status have been reported.

On rare occasions, liver function tests showed slight pathological results of transient nature (Hippius and Jantz, 1959; Telatin and Maccagnani, 1959).

The opinions on the influence of imipramine on sugar metabolism are controversial (Kuhn, 1957; Schmitt, 1959; Telatin and Maccagnani, 1959; Kaplan *et al.*, 1960).

Order

UNITED STATES COURT OF APPEALS FOR THE DISTRICT OF
COLUMBIA CIRCUIT

No. 19,706

WALTER SCHINDLER, ET AL., APPELLANTS,

v.

COMMISSIONER OF PATENTS, APPELLEE.

Appeal from the United States District Court for the
District of Columbia

Decided April 26, 1966

Mr. Caspar C. Schneider, Jr., of the bar of the Court of Appeals of New York, *pro hac vice*, by special leave of court, with whom *Mr. William A. Smith, Jr.*, was on the brief, for appellants.

Mr. Jack E. Armore, Attorney, United States Patent Office, with whom *Mr. Joseph Schimmel* Acting Solicitor, United States Patent Office, was on the brief, for appellee.

Before FAHY, *Circuit Judge*, BASTIAN, *Senior Circuit Judge*, and BURGER, *Circuit Judge*.

ORDER

This cause came on to be heard on the record on appeal from the United States District Court for the District of Columbia, and was argued by counsel, and it appearing to this Court, contrary to the finding of the trial court, that there is evidence in the record of

Order

comparative tests relating to anti-depressant activity of the compound of Claim 8 and that of Example 2 of the Schindler, *et al.* patent which is of legal significance, and that the original description does support a proffer that the compound of Claim 8 has anti-depressant properties,

Now, therefore, this Court retains jurisdiction in this appeal; and it is

ORDERED by the Court that the record on appeal herein be remanded to the District Court with directions:

(1) that it consider such evidence, described above, with such additional evidence as in its discretion and at the request of the parties it might permit to be adduced; and

(2) that it supplement the record with new findings of fact and conclusions of law, and return the enlarged record to this Court in this case.

We express no view on the merits of the appeal nor as to the effect, if any, of the above described evidence.

Per Curiam.

Motion to Dismiss Appeal

[Title omitted]

MOTION TO DISMISS APPEAL

Appellants, in the light of the Judgment entered by the District Court on February 8, 1967, setting aside its prior Judgment entered June 23, 1965, and authorizing appellee to issue a patent to appellants, now move to dismiss this appeal. Copies of the Judgment entered February 8, 1967, of the supporting Findings of Fact and Conclusions of Law, and of the District Court's opinion, are attached hereto.

WILLIAM A. SMITH, JR.
Attorney for Appellants,
William A. Smith, Jr.,
922 Woodward Building,
Washington, D.C. 20005.

Phone: 347-8070

Of Counsel:

CASPER C. SCHNEIDER, JR.,
30 Broad Street,
New York, N. Y. 10004

February 14, 1967.

Appellee's Memorandum

[Title omitted]

APPELLEE'S MEMORANDUM IN OPPOSITION TO APPELLANTS' MOTION TO DISMISS APPEAL

Appellee opposes appellants' "Motion To Dismiss Appeal." The motion is based on the entry of a judgment on February 8, 1967, setting aside a prior judgment of June 23, 1965 in defendant's (appellee) favor. Appellee asserts that the judgment of February 8, 1967 is null and void. Appellee also asserts that the original judgment should be reinstated and affirmed, as more fully set forth hereinafter.

1. This case was remanded on April 26, 1966, to the District Court for the specific purpose (1) of considering the evidence introduced at the first trial, but deemed inadmissible by the trial judge; (2) of hearing such further evidence as in its discretion and at the request of the parties it might permit to be adduced; (3) supplementing the record with findings of fact and conclusions of law, both with respect to the evidence rejected at the first trial and any new evidence adduced; and (4) of returning the enlarged record to the Court of Appeals. Finding of Fact No. 5 recognizes that this is the District Court's function at this time. Nevertheless, despite the express statement in the remand that this Court "retains jurisdiction in this appeal", the District Court, through the second trial judge, entered a final judgment that plaintiffs (appellants) are entitled to receive a patent. It is sub-

Appellee's Memorandum

mitted that this judgment should be vacated, for reasons set forth below under Point 1. It is also submitted that the original judgment should be affirmed for reasons set forth hereinafter under Point 2.

POINT 1

The decision of this Court dated April 26, 1966, held that "there is evidence in the record of comparative tests relating to anti-depressant activity of the compound of claim 8 and that of Example 2 of the Schindler et al. patent which is of legal significance, and that the original description does support a proffer that the compound of claim 8 has anti-depressant properties". Because of these holdings the Court remanded the case to the District Court to (1) "consider such evidence, described above, with such additional evidence as in its discretion and at the request of the parties it might permit to be adduced", to (2) "supplement the record with new findings of fact and conclusions of law", and to (3) "return the enlarged record" to this Court, expressly stating that "this Court retain jurisdiction in this appeal."

The clear import of this remand is that the District Court was to make findings respecting the comparative tests of record, which this Court had held to have legal significance, and to draw conclusions thereon. Also, the District Court could supplement the record with additional evidence if the parties so requested, and make findings of fact *and* conclusions based thereon as to such additional evidence, so that this Court would have the evaluation of all evidence of comparative and

Appellee's Memorandum

other tests relating to anti-depressant properties. It is also clear that all that this Court wanted the District Court to do was to make findings and conclusions, and report them to this Court.

However, instead of complying with the express conditions of the remand, the District Court, after permitting the plaintiffs (appellants) to introduce additional evidence, rendered a bench opinion (copy attached), made findings and conclusions and entered a judgment (copies attached to motion), setting aside the previous judgment of June 23, 1965, and authorizing defendant to issue a patent to the plaintiffs. Though Finding of Fact No. 5 recognizes that this Court's remand required the District Court to "return the enlarged record to the Court of Appeals", it is manifest that the record was not returned to this Court. Instead the District Court entered a final judgment. This judgment is contrary to the express wishes of this Court, as clearly evidenced by its statement that this Court "retains jurisdiction in this appeal". Without jurisdiction, it is manifest that no proper judgment could be entered by the District Court. Since jurisdiction of this appeal has been retained by this Court, and since the remand to the District Court required that findings of fact and conclusions as to all the evidence on comparative tests be submitted to this Court, the District Court clearly exceeded the authority given by the remand. Hence, the judgment entered by the District Court is null and void. In this connection, it is pointed out that the District Court had doubts as to whether

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the original evidence of comparative tests was sufficient, but the sufficiency of that evidence was not determined, though this Court had requested such a determination. The fact that the additional evidence introduced on remand was considered impressive (page 2 of opinion), did not relieve the District Court of its duty and obligation to make the findings requested by this Court. Accordingly, it is submitted that appellants' motion to dismiss should be denied. It is suggested that it would be appropriate, instead, for this Court to make its own findings and draw its own conclusions from the totality of the evidence submitted.

POINT 2

The District Court's oral Opinion on remand (copy attached hereto), states clearly that the judgment was based exclusively on new evidence adduced at the second trial. According to standards laid down by this Court, this new evidence, essentially opinions and conclusions, is of little or no probative value. It cannot legally or properly be considered the sole basis for concluding that otherwise obvious subject matter—the claimed chemical compound—which is unpatentable under 35 U.S.C. 103, becomes unobvious, and, therefore patentable. For reasons more fully explained hereinafter, it will be shown that the District Court's reliance upon this opinion evidence is contra to the criteria and standards set by this Court.

It is important to note that in the opinion of the District Court on remand, the Court expressed agreement with the Court's original decision, based upon the record made in the Patent Office, and with respect

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to the record evidence this Court desired evaluated. With respect to the latter, the Court stated that:

"The Court has doubt [emphasis added] whether that evidence, too, is sufficient to justify the conclusion of efficacy of the medicine * * *."

However, no express finding of fact relating to that evidence was made, even though this Court had expressly requested such a finding when the case was remanded. This Court in *Reynolds v. Agnides*, 123 U.S. App. D.C. 28, 356 F.2d 367, laid down the rule that "doubt [as to patentability] is to be resolved" not in favor of the applicant but "in favor of administrative * * * action." Thus, had the District Court complied with this Court's wishes as to findings and conclusions on that evidence giving full effect and force to the rule of the *Reynolds v. Agnides* case, it would have had to find that such evidence was insufficient to disturb the decision of the Patent Office that claim 8 was unpatentable, because obvious from the prior art. Having made the finding of obviousness, the District Court would then have had to conclude that claim 8 was unpatentable, since obviousness of claimed subject matter creates an absolute bar, as held in *Hays et al. v. Brenner*, 123 U.S. App. D.C. 96, 357 F.2d 287.

In concluding in the opinion "that the plaintiffs are entitled to a patent on claim 8 of their application," the District Court expressly states that it relied upon the further evidence introduced at the second trial, namely the testimony of the two witnesses, Dr. Gar-

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rone and Dr. Deniker, two professors of psychiatry, one in Geneva and the other in Paris, which the Court considered "highly impressive." Apart from the fact that that testimony sets forth only conclusions and opinions, and therefore, is of little or no probative value on the critical issue of obviousness, it must be emphasized that that testimony relates only to the use of the claimed mono-chloro compound, and does not purport to compare that compound, as to anti-depressive properties, with the closely related prior art compounds, namely the dichloro compound of the Schindler et al. patent or the non-chlorinated compound (imipramine) of the Haefliger et al. patent, referred to in Findings of Fact No. 6 (a) and (c). Such comparative results are believed to be required by this Court's decision in *Blanchard v. Ooms*, 80 U.S. App. D.C. 400, 153 F.2d 651, to justify the conclusion of patentability. Mere general opinions, even from experts, that the claimed compound is more effective or faster-acting without the comparative test evidence, upon which the opinion is based, is of no probative value on the issue of unobvious or unobviousness. This Court required such comparative testing as a pre-requisite in the *Blanchard v. Ooms* case. The Court of Customs and Patent Appeals in a number of its recent decisions, also indicates that it is in agreement, in stating that "An arguable difference is not convincing at the precise point where comparative evidence is clearly needed;" *In re Mostovych*, 52 CCPA 884, 339 F.2d 485; *In re Shannon*, 53 CCPA —, 356 F.2d 548; *In re Fortess et al.*, 54 CCPA —, 152 USPQ 13. Furthermore, if

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consideration be given that testimony, attention is invited to the fact that Dr. Garrone stated that the claimed monochloro compound was administered in 123 cases with "effective results" in about 80 percent of the cases; that Dr. Deniker stated "that he and a research group working under him had administered the medicine involved in this application to 150 patients and that its action is 'remarkable' in treating severe depressant states, apathetic schizophrenia, and severe neurotics," with about 20 percent failure; that, in addition, "at the hospital of the University of Paris the medicine has been regularly used for four years last past and several hundred patients were treated with it with success;" and that "this medicine can be used, in his opinion, in place of electric shock treatment and that it is gradually displacing electric shock treatment at the hospital of the University of Paris." The terms "effective results," and action is "remarkable," and patients were treated "with success" appear to be the evidence which the District Court considered "highly impressive." This Court has repeatedly and consistently held that results so characterized do not necessarily qualify as an advance satisfying the required standard of patentability. For example, in *Martin v. Watson*, 103 U.S. App. D.C. 106, 255 F.2d 185, "unexpectedly good results" were held insufficient; in *Darison Corp. v. Watson*, 109 U.S. App. D.C. 296, 287 F.2d 150, "important developments of substantial value to the industry" was not acceptable; in *Reinauer v. Ladd*, 110 U.S. App. D.C. 300, 293 F.2d 139 "has contributed substantially by his improve-

Appellee's Memorandum

ment" was not effective, and in *Pollack et al. v. Ladd*, 120 U.S. App. D.C. 318, 346 F.2d 799, the fact that results were "excellent" did not sway the Court to conclude that a patent should be granted. Accordingly, the District Court's failure to apply the criteria and standards of this Court in evaluating the evidence in the particular art, constitutes reversible error. Since the evidence adduced at the second trial is the sole basis for the conclusion that the compound of claim 8 is patentable over the closely related compounds of the prior art having the same property, it is submitted that the judgment should be vacated.

Furthermore, the general conclusions and opinions of the two witnesses as to the efficacy of the mono-chloro compound, which impressed the District Court, cannot properly be considered to be of any probative value. As clearly pointed out in *In re Novak*, 49 CCPA 1283, 306 F.2d 924, when utility of a drug or medicant in human therapy is alleged, it is proper to require substantiating evidence, unless one of ordinary skill in the art would accept the allegations as obviously correct. That evidence or proof of utility should be of such character as to be convincing to those skilled in the art. Later in *In re Irons*, 52 CCPA 938, F.2d 80, the same court considering claims to a material alleged to be useful in treating arthritic diseases, and methods of treating such diseases, considered this issue of proof of utility again and quotes from publications by those skilled in the art respecting the type, character and quantity of clinical testing needed to convince those skilled in the art of the efficacy of any particular new

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drug. These publications show clearly that very special controls are necessary, including "double blind tests" and proper statistical aid at the outset of the investigation. None of these factors was mentioned in the testimony of the witnesses and no clinical data was submitted. This Court also has approved the requirement for convincing proof of the asserted utility, particularly in the medical field, by requiring reports of experimentation in the laboratory or in actual use, in affirming, on the opinion of the District Court, in *Commonwealth Eng. Co. v. Ladd*, 113 U.S. App. D.C. 53, 304 F. 2d 630. Additional authoritative publications respecting the necessity of controlled testing in the medical arts in general is called to the Court's attention. If deemed necessary, the Court could judicially notice the following statement in the authoritative work "The Pharmacological Basis of Therapeutics," edited by Goodman and Gilman (The Macmillan Company, New York, 1965), appearing on page 162 of chapter 12 (entitled "Drugs Used in the Treatment of Psychiatric Disorders," by Murray E. Jarvik):

Clinical Assessment of Pharmacotherapy. One of the most difficult problems in psychiatry is the assessment of therapy, and this is true whether the treatment is psychological, physical, or chemical. One must somehow answer the questions whether the patient is improved after treatment and whether improvement is due to the treatment. One must be particularly careful to rule out the possibility that a natural remission has occurred, or that the patient or personnel connected with the

Appellee's Memorandum

therapeutic trial have been influenced somehow by factors other than the specific treatment in question. Criteria for the evaluation of results in psychotherapy have varied from intuitive subjective generalizations of therapists or patients, through rating scales, to objective measures of behavioral change in patients.

The advent of clinical psychopharmacology in the 1950s provided a tremendous impetus for the development of objective technics to measure behavioral pathology in large groups of patients. Drugs have the virtue over other forms of therapy that they are discrete material substances that can be measured and easily dispensed in a controlled fashion. Psychotherapy, shock therapy, or surgery could not be studied in this controlled manner. New scales and inventories to evaluate psychopathology, including those by Burdock, Wittenborn, and Loor, were designed specifically to deal with large state-hospital populations. Modifications of the anxiety scale on the Minnesota multiphasic personality inventory (MMPI) were devised and used to evaluate drugs such as meprobamate and chlordiazepoxide; the depression scales of the MMPI have been employed to measure effects of monoamine oxidase inhibitors and imipramine, and a number of specialized depression scales have been developed.

Drugs also stimulated investigators to become more concerned about scientific methodology and the need for proper controls (see U.S. Dept. of

Appellee's Memorandum

Health, Education, and Welfare, 1962). The use of matched samples of patients receiving different drugs or placebos and of crossover designs in which the same patients were given different treatments several times according to a balanced design became feasible with pharmacological agents. Untreated controls have been used to measure spontaneous change in psychiatric status, although such patients are increasingly difficult to find.

Experimenters or subjects can intentionally or unintentionally introduce bias into an investigation by preconceived ideas of what results can be expected. This might be considered the influence of suggestion or autosuggestion, similar in most respects to that seen with hypnosis. What is commonly called the placebo response may be interpreted as the result of a preconceived idea or of the suggestion made by another individual that a particular tablet, capsule, or injection would have a particular effect. Whether high suggestibility is characteristic of a certain class of people (placebo reactors) has been a subject of some controversy. There is no question that the true pharmacological effect of drugs may be intensified or nullified by suggestion. Thus, by appropriate instructions, amphetamine has been observed to sedate patients and barbiturates to stimulate them (Ross *et al.*, 1962; Frankenhaeuser *et al.*, 1963). Raters who have been influenced to expect certain effects from drugs often find them, even when placebos have been given. In order to eliminate

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bias, the double-blind procedure has been widely applied to drug experiments. With this technic, both experimenter and subject are kept as ignorant as possible of the nature of the drugs being administered and someone not otherwise involved keeps the key to the drug code until the end of the experiment. Often drugs reveal their presence through strong side effects, but sometimes active placebos (i.e. those with similar side effects but no therapeutic action) may be employed to advantage. Numerous review of the placebo problem are available (see Wolf, 1959; Joyce, 1961).

Since suggestion can play a major role in psychotherapy, a critique of experimental design will often be included in the following discussions of the individual drugs, and descriptions of clinical effects will rely heavily on the results obtained in well-controlled rather than uncontrolled studies.

It is manifest from the above statement by Jarvik that the minimum requirements for establishing the efficacy of a drug (especially a psychiatric drug) include the use of recognized objective standard test procedures (such as the "depression [rating] scales of the MMPI" referred to by Jarvik) and the utilization of effective controls. There is no evidence that these minimum requirements were met in the tests generally alluded to by the two witnesses. Moreover, in enacting the Food and Drugs statutes (Title 21, United States Code), the Congress specified the type of evidence it considered necessary to establish the efficacy (as well as safety)

Appellee's Memorandum

of new drugs. Thus, 21 U.S.C. 355 provides in pertinent portions, that:

(b) * * * Such person shall submit to the Secretary as part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is as effective in use * * *.

* * * * *

(d) [An application may be disapproved where]

(5) * * * there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have * * *.

* * * the term "substantial evidence" means evidence consisting of adequate and well controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have * * *.

Consequently, albeit in a non-patent statute, Congress expressed its sense of the evidence it considers necessary to establish the efficacy (and safety of drugs). Where, as here, efficacy of a drug is sought to be established by applicants to justify the grant of a patent, it is reasonable to presume that the standard of evidence suggested by Congress should be followed.

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Clearly, the general testimony of Drs. Garrone and Deniker does not meet the standards of evidence set out in 21 U.S.C. 355 as indicated above. It may be noted too, that probative evidence of efficacy (as is apparent from 21 U.S.C. 355) requires the submission of the raw test data (including actual clinical reports) so that the conclusion of the witnesses may be compared with the actual test results; no such data was submitted to corroborate the witnesses' testimony.

Since the appellants introduced no probative evidence of comparative tests with the prior art compounds at the second trial, and since the general testimony of efficacy—in addition to lacking probative value—does not establish patentable superiority over the prior art drugs, there is no basis for holding the claimed compound patentable in view of the entire record in the case. On this basis, too, the appellants' motion to dismiss the appeal should be denied and the first judgment appealed from, the only legally valid judgment in the case, should be affirmed.

Respectfully submitted,

JOSEPH SCHIMMEL,
Solicitor, United States Patent Office,
Attorney for Appellee.

JACK E. ARMORE,
Of Counsel.

FEB. 20, 1967.

Appellants' Reply to Appellee

UNITED STATES COURT OF APPEALS FOR THE DISTRICT
OF COLUMBIA CIRCUIT

APPEAL No. 19,706

WALTER SCHINDLER and HENRI DIETRICH, APPELLANTS,

v.

COMMISSIONER OF PATENTS, APPELLEE.

APPELLANTS' REPLY TO APPELLEE'S MEMORANDUM IN
OPPOSITION TO APPELLANTS' MOTION TO DISMISS THIS
APPEAL.

Appellants' Reply to Appellee

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COMMISSIONER OF PATENTS, APPELLEE.

APPELLANTS' REPLY TO APPELLEE'S MEMORANDUM IN
OPPOSITION TO APPELLANTS' MOTION TO DISMISS THIS
APPEAL.

I. Introduction:

A. History

This is a suit under 35 U.S.C. 145 against the Commissioner of Patents to authorize him to issue a patent to plaintiffs-appellants on a new chemical compound useful in the treatment of mental depression.

The case first came on for trial in February, 1965. At that trial, evidence of the anti-depressant properties of the compound was introduced. The District Court held that it could not consider the evidence of anti-depressant use because such use was not properly disclosed in the application and hence found for the defendant.

On appeal, this court held that the application was adequate to support a proffer of evidence of anti-depressant properties, and remanded the case to the District Court with instructions to consider the evi-

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dence previously adduced, together with new evidence, if it wished to accept such new evidence.

A second trial was held on January 11, 1967, and the District Court made new findings of fact and conclusions of law favorable to plaintiffs. Defendant moved to add further findings, but at a hearing held February 8, 1967, this motion was denied and the District Court entered a judgment in favor of plaintiffs.

With this record, plaintiffs-appellants on February 14, 1967, moved to dismiss its appeal. In a memorandum dated February 20, 1967, appellee opposed the motion.

In this reply to defendant-appellee's memorandum, we refer to the transcript on the second trial (January 11, 1967) as (Tr.). The transcript of the hearing on defendant's motion to add findings of fact (February 8, 1967) was made by a different reporter and is independently paginated. It is referred to as (Tr. Hearing). The Joint Appendix is referred to as (JA).

B. Analysis of Appellee's Argument

Appellee's attack on appellants' motion to dismiss this appeal breaks down into two parts, the procedural and the substantive. In the first place, appellee argues that the District Court had no authority to enter a judgment; and in the second place that the judgment and the findings and conclusions which support it, were erroneous.

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II. The Procedural Question:

A. *The District Court Properly Entered a New Judgment*

In its Order remanding the case to the District Court, this Court gave directions:

"(1) that it consider such evidence, described above, with such additional evidence as in its discretion and at the request of the parties it might permit to be adduced; and

(2) that it supplement the record with new findings of fact and conclusions of law, and return the enlarged record to this Court in this case."

On the second trial, further evidence, including evidence of anti-depressant use, was introduced. As we have noted, the District Court made new findings of fact and conclusions and law, and the record has been returned to this Court, all in accordance with the directions on remand.

The finding of the District Court on remand was that the compound in question was unobvious; and its conclusion was that the compound was patentable. These were obviously in conflict with the judgment previously entered. The District Court was thus faced with returning to this Court a record which, on its face, would require reversal of its judgment of record. Faced with this incongruity, the District Court took the most rational course. It set aside the judgment previously entered and entered a new judgment in favor of appellants-plaintiffs consistent with the new findings and conclusions it had made.

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Appellee argues that the District Court exceeded its authority in entering judgment since this Court retained jurisdiction. It is submitted, however, that the authority to enter a new judgment was implicit in the mandate, because the mandate must have contemplated the possibility that the new findings of fact and conclusions of law might be favorable to appellants. In such case, the findings would be inconsistent with the judgment of record, and would lead to the incongruous situation referred to.

The District Court followed the most rational course open to it and its entry of judgment was wholly proper.

B. The Record Has Been Returned to this Court

Appellee has also asserted that the District Court did not return the enlarged record to this Court. Appellants have been assured that the record has now been returned.

C. The District Court's Findings of Fact were Complete

Appellee has also asserted that the District Court did not comply with the directions on remand because it made no determination on the question of whether the evidence of comparative tests presented at the first trial was sufficient in itself. Appellants find no such direction in this Court's remand order. Findings of fact should be brief, definite and pertinent. As this Court pointed out in *Klimkiewicz v. Westminster Deposit & Trust Co.*, 122 F. 2d 957, 958 (App. D.C. 1941); cert. den. 315 U.S. 805 (1942), a trial court need only find such ultimate facts as are necessary to reach its

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decision. See also *Schilling et al. v. Schwitzer-Cummins Co.*, 142 F.2d 82, (App. D.C. 1944) and *Norwich Indemnity Co. v. Haas*, 179 F.2d 827, 7 Cir. (1950). Clearly the question of what the District Court *might* have decided on the Patent Office record, or on the record after the first trial, was not necessary to its decision here.

Furthermore, it is clear that the District Court reached its conclusion on the basis of the *whole* record. This was specifically stated by the Court in denying defendant-appellee's request to make additional findings of fact. (Tr. Hearing 4).

III. Issues of Substance

Appellee, in "Point 2" of his memorandum, attacks the findings of fact made by the District Court. This attack is unsupportable.

We start from Rule 52(a) which requires that in cases tried upon the facts without a jury

"... Findings of fact shall not be set aside unless clearly erroneous, and due regard shall be given to the opportunity of the trial court to judge of the credibility of the witnesses ..."

Appellee has failed to show that the District Court's findings are "clearly erroneous".

The burden of appellee's case appears to be that the Court would not have found for the plaintiffs-appellants on the basis of the record at the conclusion of the first trial; that the evidence adduced at the second trial was insufficient as a matter of law and that, therefore, the decision of the District Court is improper.

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This argument is specious on its face. The evidence cannot be considered piecemeal. It is cumulative and must be considered as a whole. When considered as a whole, it is clear that the District Court's decision was correct.

Replying to the specific points raised by the Appellee:

A. The District Court, specifically, did *not* determine whether the evidence produced during the first trial would or would not have been sufficient to demonstrate anti-depressive properties. It said (Tr. 154):

"If the record before this Court consisted solely of the record before the Patent Office, this Court would be inclined to sustain the decision of the Patent Office. Additional evidence was introduced at the first trial of tests performed on patients, with a successful result. The Court has doubt whether that evidence, too, is sufficient to justify the conclusion of efficacy of the medicine, *but the sufficiency vel non of that particular evidence need not be determined* because at this hearing further evidence was introduced which the Court considers highly impressive." (Emphasis added)

B. The Court's decision was *not* "based exclusively on new evidence adduced at the second trial" as asserted by appellee. While the Court said (Tr. 159) that it was "acting solely on the basis of additional evidence", this had reference to the Patent Office record. In fact, the Court specifically pointed out to Counsel for Appellee that it had considered *the record as a whole*. (Tr. Hearing 4).

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C. The appellee criticizes the testimony of Dr. Garonne and Dr. Deniker, who testified at the second trial, as consisting of "conclusions and opinions". This is not a fair assessment. Both witnesses testified that they had used the drug in hundreds of cases (Tr. 95, 111, 112) and that it was being used in clinics in Geneva and Paris (JA 98; Tr. 95, 111, 112). This is neither opinion nor conclusion, but fact. Dr. Garonne referred to his affidavit of record in the case (JA 96). This affidavit sets forth details of treatment of twenty-three patients. Dr. Garonne testified that his experiences with additional patients (over 100) bear out the results reported in that affidavit (Tr. 96). He specifically reaffirmed his finding that the latency period is less than that of any similar drug, including the only drug shown in the prior art of record, which has been demonstrated to have anti-depressant effects (JA 107; Tr. 95-97). This is not opinion, but fact, and data on latency periods for the claimed compound is given in Garonne's affidavit. Further, Dr. Garonne testified that the dosage for the claimed compound was about 75 mg. per day whereas the dosage of imipramine (the prior art depressant referred to) was 150-200 mg./day. Again this is not opinion, but fact.

Professor Deniker testified that the claimed compound had been used for the past four years at the hospital of the University of Paris (Tr. 111). This was not a conclusion or opinion, but fact. He further testified that he had used the drug to replace electroshock therapy (Tr. 112, 113, 119). This was not opinion or conclusion, but fact. He further testified that he

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knew of no other anti-depressant that could be so used (Tr. 113, 114). While the weight accorded this statement is affected by the authority of the speaker, it is a factual statement.

D. Appellee complains that the testimony did not compare the compound at issue with the two prior art compounds, dichlorimipramine (the Schindler patent) or imipramine (the Haefliger patent).

Dichlorimipramine was compared with the claimed compound by the witness Poldinger at the first trial (JA 61-68). Dr. Poldinger testified that the compound is useless as an anti-depressant. There is no evidence to the contrary.

Imipramine is an anti-depressant. However, Dr. Garonne testified that the compound claimed has a much shorter latency period (Tr. 97), and that this is particularly important in treating depression where suicide is an ever-present danger. He and Prof. Deniker agreed that the dosage of the claimed compound was about half that of imipramine. (Tr. 97, 98, 118). He also stated that it has less side effects.

Dr. Deniker pointed out that while the claimed compound is being used to replace electro-shock treatment in severe depressions, imipramine cannot be used for this purpose (Tr. 112, 113, 119).

This is, in fact, evidence comparing the prior art with the claimed compound. That numerical data was not presented as to imipramine is scarcely surprising since notice of the Patent Office's intention to rely on that compound was not given until six days before trial. The fact is that both witnesses, experts in their field,

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were familiar with both compounds and so were able to testify, from their experience, on the differences between them. The situation is, therefore, quite different from that in *Blanchard v. Ooms*, 80 App. D.C. 400, 153 F.2d 651, and the other cases cited by appellee where there was no comparative evidence by independent experts in the record.

E. Appellee criticizes the testimony of the witnesses as too general in characterizing the effects of the compound as "remarkable" and "highly impressive." Those terms, however, were supported by the factual testimony referred to above. As we have noted, the witnesses reported that the drug was being used and had been used under their supervision in hundreds of cases; that it was effective in various types of depressions; was more rapid in action, at lower dosages, than the prior art anti-depressant of record and, unlike that prior art compound, could be used to replace electroshock therapy. This is not vague and general "puffing," but clear and certain endorsement from practicing psychiatrists of international stature.

The cases cited by appellee, *Martin v. Watson*, 133 App. D.C. 106, 255 F. 2d 184; *Darison Corp. v. Watson*, 109 App. D.C. 296, 287 F. 2d 150; *Reinauer v. Ladd*, 100 App. D.C. 300, 293 F. 2d 139; and *Pollack et al. v. Ladd*, 120 App. D.C. 318, 346 F. 2d 999 have no applicability here. All of those cases involved findings by the District Court adverse to the applicants which this Court felt it could not say were "clearly erroneous." Moreover, all involved instances where there was a serious question of *novelty*. In *Martin* the process in-

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volved using a critical gas injection pressure to recover oil from sands. The Court noted (F. 2d 185) that this very pressure was contemplated by a prior art patent. In *Darison* the claims involved applying an old testing technique to milk. Broad claims were denied but specific claims applicable only to milk were allowed. In *Reinauer* the subject matter involved cleaning air filters, and it appears that the elements relied on for distinguishing over the prior art were inherently present in it. (Cf. F. 2d P. 140). In *Pollack* this Court agreed with the District Judge that "each of the claims was directly readable upon prior art."

Under the circumstances obtaining in these cases, of course, no amount of commercial success could result in patentability. Here, however, there is no question of novelty, and the District Judge, having had the opportunity to hear and observe the witnesses, found that the differences between the prior art and the claimed compound was so great as to amount to a new result. There was no comparable finding in the cited cases.

F. Appellee further asserts that in the case of medicaments, substantiating evidence should be introduced, including "double blind tests". The two cases relied upon to support this argument are not effective for the purpose. *In re Novak et al.*, 49 CCPA 1283, 306 F. 2d 924 (1962) represented a case in which there were claimed certain new bases of pharmaceutically active compounds such as streptomycin. The assertion was that by administering such compounds in the form of the claimed bases it became possible to control the physiological response to the compound. The record, how-

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ever, was absolutely devoid of *any* showing that the new compounds would have the properties asserted. For this reason, the Court affirmed the Patent Office rejection on lack of proof of utility.

Here, of course, the rejection is not on lack of utility and the record is ample to show that the compounds are in fact being used as anti-depressants.

In re Irons, 52 CCPA 938, 340 F.2d 974 (1965) involved a preparation asserted to be useful in treating arthritis. The claims were rejected for lack of utility. The record contained:

(a) Five examples in the application showing administration of the compound to arthritics with good results.

(b) Letters from two physicians indicating that over 800 patients had been treated with improvement in about 95% of the cases.

(c) A publication giving 10 case histories in all of which some improvement was noted.

The Patent Office held that this evidence was insufficient because "double blind" tests were not used and because the "placebo factor" was not taken into account. The CCPA reversed, pointing out that "historical" controls, i.e., those in which the history of the patient is known, as well as "double blind" controls, are accepted by medical authorities.

It is of course well settled that the kind of tests required depends upon the situation. *In re Hartop*, 311 F.2d 249, 135 USPQ 419. Here Dr. Deniker (TR. 120) and Dr. Garonne (Tr. 102, 103) testified that these

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patients were observed for extended periods before and after administering the drug. Dr. Garonne (R. 103) indicated that the placebo factor was not significant in depressed patients, and Dr. Deniker indicated that his clinic definitely rejected the use of placebos. (Tr. 120). Note also the testimony of Dr. Poldinger on the ethical points involved (JA 70-71).

Clearly the tests administered by the witnesses were proper and sufficient to demonstrate the properties of the claimed compound.

Appellee also referred to this Court's decision in *Commonwealth v. Ladd*, 133 App. D.C. 53, 304 F. 2d 630 (1962), affirming the District Court's decision reported at 199 F. Supp. 51. We point out that the District Court in *Commonwealth* was the same as in the second trial in this case. The Court was fully appreciative of the significance of *Commonwealth*, referring to it at the opening of the trial, (Tr. 45) and in its opinion (Tr. 156). It lends greater strength to appellants' case that the Court, despite its conservative attitude toward medical patents, found the record in this case to be so clearly convincing as to justify a patent grant.

G. Appellee's quote at length from an article by M. E. Jarvik in a text issued in 1965 on the need for controls in testing psychopharmaceuticals. Consideration of this material is clearly improper. Appellee relies upon the opinion of the author who is not available for cross-examination and whose credentials are not presented. No opportunity for interpretative or contradictory testimony has been offered.

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Appellants agree that the evaluation of psychopharmaceuticals is difficult. However, considering the professional stature of the witnesses, the number of patients they treated and the fact that the histories of patients both before and after treatment were known, the likelihood of the placebo factors being responsible for the results reported is not reasonable.

H. Appellee attempts to assert that the FDA requirements for the marketing of a new drug should be imposed on inventors seeking to patent a new drug. This position has no foundation in statute or precedent. The purposes of the food and drug laws and the patent laws are different. The patent laws are aimed at the advancement of the useful arts. In meeting that objective, one desideratum is the early publication and disclosure of inventions. The food and drug laws on the other hand are primarily concerned with protecting the consumer. In line with this objective, the tests required for FDA approval involve far longer times than would be desirable in the Patent Office. If every pharmaceutical patent application were required to be supported by FDA type data, virtually all such applications would be finally rejected long before the data became available. This is particularly true with inventions made abroad, where patent applications must be filed immediately, since the patent goes to the first-to-file, not to the first inventor.

There is nothing whatever in the patent laws or Rules of Practice which lay down any such requirement as appellee now urges; nor is any such requirement derivable from the case law. *In re Hartop*, cited above.

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The section of the Food Drug and Cosmetic Act (21 U.S.C. 355), quoted by appellants, is explicit as to the standards to be met before new drugs may be introduced into commerce. The Secretary of Health, Education and Welfare has promulgated in extensó detailed regulations setting out the nature of the data to be supplied to obtain new drug approval (New Drug Regulations, Section 130.4).

The Patent Act, on the other hand, (35 U.S.C.) sets out no specific requirements for the type of data to be supplied in establishing patentability. The Commissioner of Patents has promulgated Rules of Practice (37 C.F.R.) governing practice before the Patent Office. There is nothing in these rules which would require explicitly or by implication the kind of data appellee now demands.

Appellants respectfully submit that it is clearly arbitrary, in the absence of any regulation even remotely resembling those published under the Food Drug and Cosmetic Act, for appellee now to insist that data of this nature is necessary to establish patentability.

As a matter of fact, however, the standards set down by appellees in their quotation from 21 U.S.C. 355 have been substantially met by appellants. The psychiatrists who testified were amply qualified for their task, and controls were employed in the sense that the history of the patients was known and their progress after administration of the drug was observed. That the type of controls advocated by the Patent Office was not used or that raw data was not submitted, does not alter the fact that the drug has been investigated by qualified

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experts who fairly and responsibly concluded that the drug has the effect it is represented to have.

I. The requirements of the patent law are novelty, utility and unobviousness. There is no question here of novelty—the compound is concededly new. There is no real question as to utility. The testimony of three eminent psychiatrists that it is in use in large metropolitan clinics can hardly be brushed aside. As to obviousness, the closest prior art compounds are the dichloro analogue of the present compound (the Schindler patent) and the non-chlorine containing analogue (the Haeffiger patent). The dichloro compound, which was the chief prior art relied upon by appellee up until a few days before the second trial, is not an anti-depressant. This is established by pharmacological tests on animals (the Sigg testimony, JA 53-56) and clinical tests on human beings (the Poldinger testimony, PA 66). There is no contrary evidence.

The non-chlorine containing compound is an anti-depressant and has been used as such since about 1957. It is described in the Haeffiger patent (1951) of which the Patent Office must have been aware. Yet so little was the Examiner impressed by this that no reliance was placed upon it until the second trial, appellants' counsel having been informed of the Office's intention on Thursday, January 5, just six days before trial.

If one considers these two prior art compounds together, the *obvious* conclusion is that the introduction of chlorine into the molecule eliminates anti-depressive activity, since the dichloro compound is wholly lacking in that quality. It was certainly not clear, plain or

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obvious that adding one chlorine atom at a particular position in the molecule would not only give a useful anti-depressant, but one having a shorter period of latency at roughly half the dose and the remarkable property, attested to by Professor Deniker, of enabling electro-shock treatment to be replaced in cases of severe depression.

The District Court was clearly justified in its revised findings and conclusions of law and in its judgment.

The appeal should be dismissed.

WILLIAM A. SMITH, JR.,
Attorney for Appellants.
William A. Smith, Jr.,
922 Woodward Building,
Washington, D. C. 20005.

Phone: 347-8070.

March 13, 1967

Of Counsel:

CASPAR C. SCHNEIDER, JR.,
30 Broad Street,
New York, N.Y. 10004.

Order

UNITED STATES COURT OF APPEALS FOR THE DISTRICT OF
COLUMBIA CIRCUIT

No. 19,706

September Term, 1966

Civil 3068-63

WALTER SCHINDLER, et al., APPELLANTS,

v.

COMMISSIONER OF PATENTS, APPELLEE

Before: Fahy,* Circuit Judge, and Bastian, Senior
Circuit Judge, and Burger, Circuit Judge, in Chambers.

ORDER

It appearing that on April 26, 1966, this court remanded this case for further proceedings with directions to the District Court to supplement the record with further findings of fact and conclusions of law, this court retaining jurisdiction with directions to the District Court to return the enlarged record to this court, and

It further appearing that upon conclusion of the remanded proceedings the District Court on February 8, 1967, set aside its judgment in favor of appellee of June 23, 1965, and entered a judgment in favor of appellant, now

On consideration of appellant's motion to dismiss this appeal, appellee's opposition, appellant's reply

* Circuit Judge Fahy became a Senior Circuit Judge on April 13, 1967.

Order

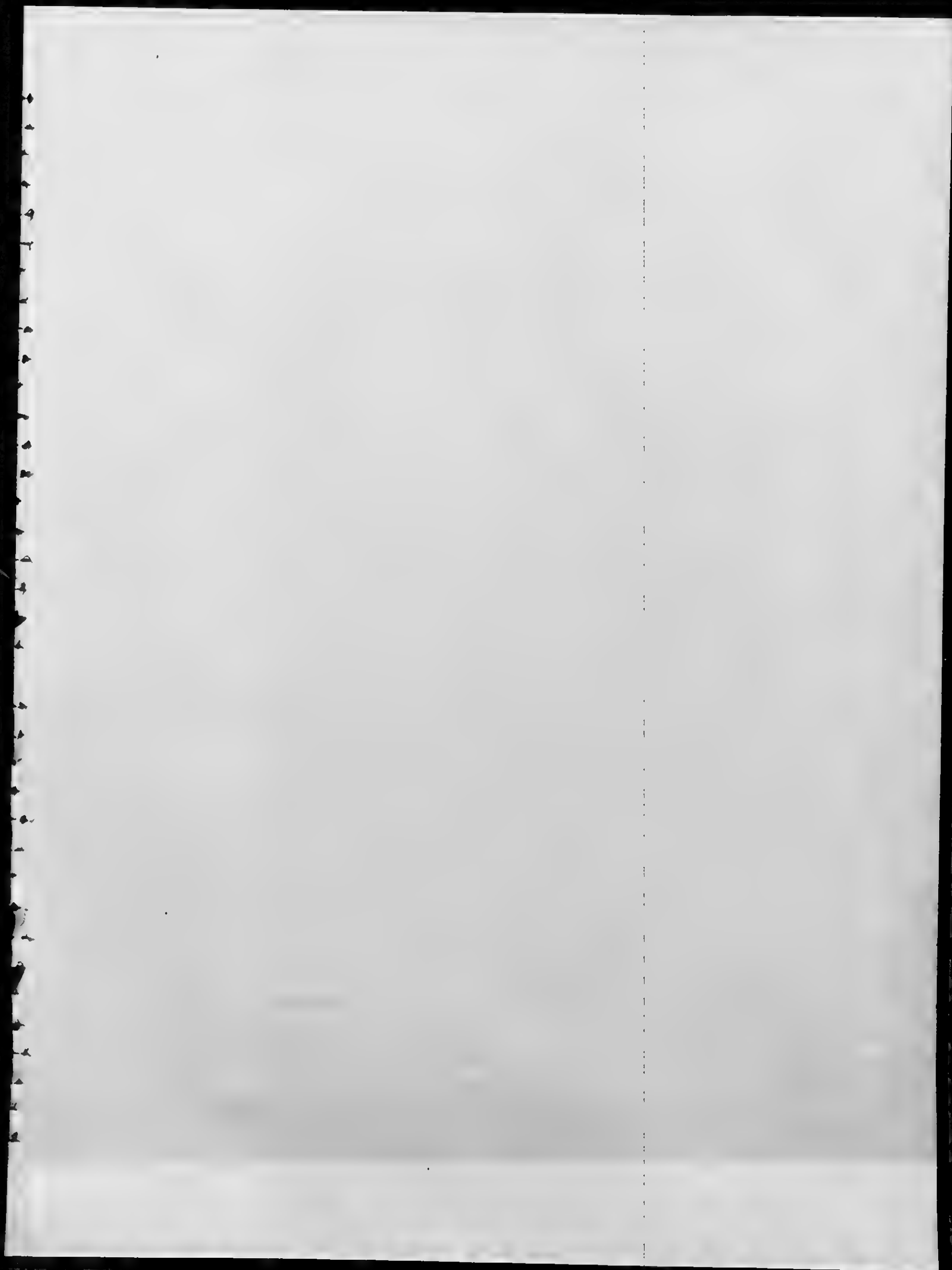
thereto, the original record, and the supplemental record filed pursuant to this court's order of April 26, 1966, it is

ORDERED AND ADJUDGED that appellant's motion to dismiss the appeal is denied, and it is further

ORDERED that the judgment of February 8, 1967, is vacated and this case is remanded to the District Court in order that it may enter now such judgment as it deems appropriate in the circumstances.

Per Curiam.

Dated: May 24, 1967.



BRIEF FOR APPELLANT

IN THE
United States Court of Appeals
FOR THE DISTRICT OF COLUMBIA CIRCUIT

No. 21,309

COMMISSIONER OF PATENTS, APPELLANT

v.

WALTER SCHINDLER ET AL, APPELLEE

**APPEAL FROM THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA**

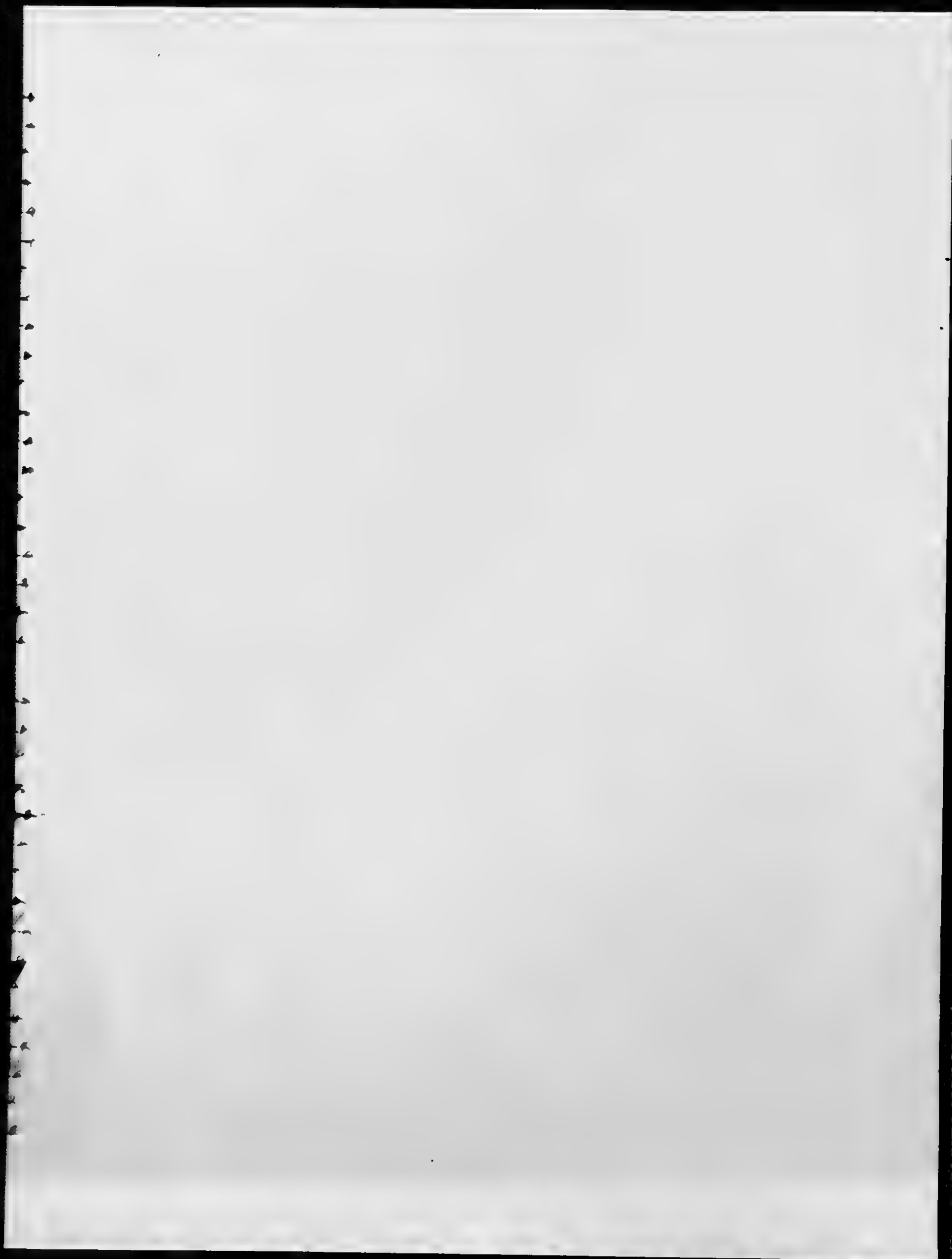
JOSEPH SCHIMMEL,
Solicitor, United States Patent Office

JACK E. ARMORE,
Of Counsel

United States Court of Appeals
for the District of Columbia Circuit

FILED NOV 30 1967

Nathan J. Paulson
CLERK



STATEMENT OF QUESTIONS PRESENTED

The questions presented in this appeal are:

1. Since the District Court's oral opinion states that the judgment was based exclusively on new evidence introduced at the second trial, specifically the testimony of Dr. Garrone and Dr. Deniker, did that Court err in attributing probative value to that testimony which amounts to no more than conclusions and opinions?
2. Since the District Court's oral opinion indicates that the judgment was based exclusively on the testimony of Drs. Garrone and Deniker at the second trial because it "was very strong in showing the superior efficacy" of the claimed compound, did that Court err as a matter of law because that testimony did not meet the requirement laid down by this Court in *Blanchard v. Ooms*, 80 U.S. App. D.C. 400, for comparative tests between the claimed subject matter (compound) and the closely related prior art compounds?
3. Did the District Court manifestly err in failing to hold that the claimed compound would have been obvious to one of ordinary skill in the art from the teachings of the prior art, and therefore unpatentable?
4. Did the District Court err, as a matter of law, in failing to hold that the claimed compound, asserted to be an anti-depressant, was obvious and therefore unpatentable in view of the known chemically closely related anti-depressant compound of the prior art.

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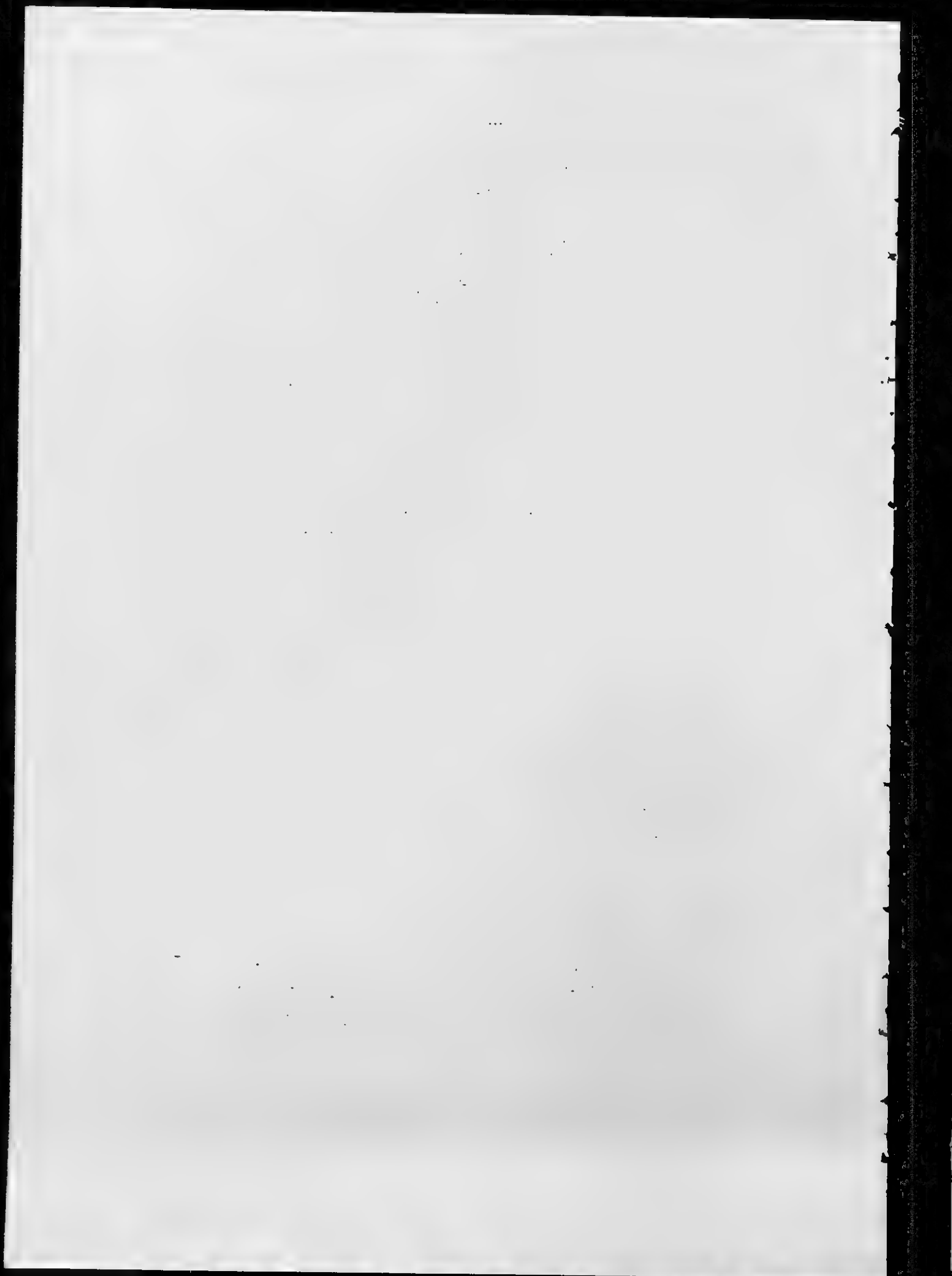
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Appeal No. 21,309

COMMISSIONER OF PATENTS, APPELLANT

v.

WALTER SCHINDLER ET AL, APPELLEE

*APPEAL FROM THE FINAL JUDGMENT OF THE UNITED
STATES DISTRICT COURT FOR THE DISTRICT OF COLUMBIA*

BRIEF FOR APPELLANT

INTRODUCTION

This is an appeal from the order of the United States District Court for the District of Columbia dated June 20, 1967 (JA-250) in which the defendant (appellant) was authorized to issue a patent to the plaintiffs containing claim 8 of patent application Serial No. 857,274, filed by Walter Schindler and Henri Dietrich on December 4, 1959, entitled "New N-Heterocyclic Compounds". The Notice of Appeal (JA-252) was timely filed on August 18, 1967.

This action was instituted by a complaint (JA-2) filed by plaintiffs under the provisions of 66 Stat. 803, Title 35 U.S.C., Section 145. This Court has jurisdic-

tion with respect to appeals from final orders of the District Court by virtue of 62 Stat. 869, Title 28 U.S.C., Section 1261.

HISTORY OF THE CASE

The complaint sought to have the District Court authorize the issuance of a patent containing certain claims (JA-2 to 4). The case came on for a first trial on February 16, 1965; at that time, appellants withdrew all claims from suit except claim 8, thus leaving only that claim at issue before the District Court (JA-140). In an opinion dated June 23, 1965 (JA-140), "[a]fter reviewing the evidence presented, and considering the briefs the parties were accorded an opportunity to file", the District Court found that the compound of claim 8 "would have been obvious to one of ordinary skill in the art at the time the plaintiffs filed their application from the combined teachings of Schindler et al and the Australian patent" (Finding of Fact 12; JA-142), that "the evidence of comparative tests relating to anti-depressant activity of the compound of claim 8 - - - - is of no legal significance, since it is based on an advantage or property for the claimed compound which is undisclosed in the application as filed - - - -" (Finding of Fact 10; JA-142), and dismissed the complaint (JA-144).

The plaintiffs appealed to this Court—Appeal No. 19,706 (JA-145). In an order dated April 26, 1966, this Court held:

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that there is evidence in the record of comparative tests relating to the anti-depressant activity of the

compound of claim 8 and that of Example 2 of the Schindler et al patent which is of legal significance, and that the original description does support a proffer that the compound of claim 8 has antidepressant properties * * *.

This Court retained jurisdiction in the appeal and remanded the case to the District Court with directions to consider the evidence referred to above, together with additional evidence it might permit to be adduced, to "supplement the record with new findings of fact and conclusions of law, and return the enlarged record to this Court in this case".

A second trial was held on January 11 and 12, 1967, during which both parties introduced additional evidence. At its conclusion, the District Court rendered an oral opinion (JA-234) holding the claimed compound unobvious from the prior art, and patentable thereover, based expressly and exclusively on the testimony of Drs. Garrone and Deniker. On February 8, 1967, the District Court signed findings of fact and conclusions of law favorable to the plaintiffs (JA-246) and a corresponding Judgment setting aside the prior District Court Order of June 23, 1965. The Commissioner appealed.

The appellants-plaintiffs moved to dismiss Appeal No. 19,706 on February 14, 1967 (JA-279). On February 20, 1967, the defendant below filed Appellee's Memorandum In Opposition to Appellants' Motion to Dismiss Appeal (JA-280); appellants filed a reply on March 13, 1967 (JA-294). In an Order dated May 24, 1967 (JA-313), this Court denied appellants' motion to dismiss the appeal, vacated the District Court Judg-

ment of February 8, 1967, and remanded the case to the District Court "in order that it may enter now such judgment as it deemed appropriate in the circumstances". The District Court entered a Judgment favorable to the plaintiffs on June 20, 1967 with no further opinion or findings of fact and conclusions of law (JA-250). As previously indicated, the defendant below filed a Notice of Appeal on August 18, 1967 (JA-252) commencing present Appeal No. 21,309.

APPELLEE'S BRIEF IN APPEAL NO. 19,706

As indicated, the appellant-appellee relationship of the parties in Appeal No. 19,706 has been reversed in the present appeal. To the extent relevant, and as indicated below, the present appellant will rely upon his (the appellee's) brief in Appeal No. 19,706; that brief will be referred to as (App. Br. —) hereinafter. The Joint Appendix in Appeal No. 19,706 is Part I (with the same pagination) of the Joint Appendix in the present appeal.

APPELLEE'S APPLICATION

The relevant disclosure in the application at bar is described in (App. Br.-2 and 3) under "Appellants Application".

THE CLAIM IN ISSUE

Claim 8 (JA-80, page 16), the sole claim in issue, is directed to a single compound, namely, 3-chloro-5-dimethylaminopropyl) iminodibenzyl having the structural formula shown in the defendant's chart (Def. Ex. 2 J.A.-136).

This claim was rejected by the Patent Office as obvious from the patent to Schindler et al, granted Novem-

ber 19, 1957, in view of the Australian patent 215,335 granted June 11, 1958. The claim is also considered unpatentable over the chemically closely related well-known anti-depressant compound *imipramine* disclosed by the Haefliger et al patent 2,554,736, granted May 29, 1951, and the German article by Kuhn (with an English summary; 1957).

THE PRIOR ART

The Schindler et al patent (JA-126) and the Australian patent (JA-128) are described in (App. Br. 4 and 5) under "The Prior Art".

Haefliger et al (JA-255) disclose a class of unchlorinated 5-substituted-iminodibenzyl compounds corresponding closely to the similar class of compounds disclosed by the appellees (JA-80, page 1); the compounds are said to possess "valuable pharmacological properties" as, "for instance, they produce anti-allergic effects" (col. 4, second paragraph). The patentee specifically disclose N-(γ -dimethylaminopropyl)-iminodibenzyl, which is also known as imipramine (col. 3, lines 43 and 44).

Kuhn (JA-267) in the English "Summary" at the end of his article, discloses that imipramine (identified by its chemical name and as G22355) is a highly effective anti-depressant, that "success may be expected in three-quarters to four-fifths of cases", and that "Even cases resistant to *shock therapy* may respond" (emphasis added). Kuhn also states that "The drug is in general well tolerated" and it is indicated that there are no serious or severe side-effects.

SUMMARY OF ARGUMENT

1. The testimony of Drs. Garrone and Deniker does not establish *superior* efficacy as an anti-depressant for the claimed monochloro compound since *that testimony does not purport to have compared* (by actual comparative tests) that compound with the closely related prior art compounds (the dichloro compound of the Schindler et al patent and the unchlorinated compound of the Haefliger et al patent or the Kuhn publication).

2. The District Court, in its oral opinion (JA-232), clearly indicated that the testimony of Drs. Garrone and Deniker was the *sole basis* for holding that the claimed compound was unobvious and therefore patentable over the prior art. However, that testimony has no probative value since it is *not based on primary factual evidence* and therefore it amounts to no more than unsupported conclusions or opinions.

3. The *concept* of the claimed monochloro compound would have been obvious to one of ordinary skill in the art from the corresponding dichloro compound of Schindler et al in view of the teaching in the Australian patent that a *host* of similar compounds may be unsubstituted, monohalogen substituted or dihalogen substituted in the iminodibenzyl nucleus, especially since the compounds are so closely related in chemical structure and the patents disclose closely related as well as overlapping pharmacological properties for the classes of compounds disclosed.

4. The claimed monochloro compound does not distinguish patentably over the corresponding unchlorinated (thus chemically very closely related) well-known anti-depressant compound *imipramine* disclosed by Haefliger et al and Kuhn; especially since Kuhn points

to the high degree of efficacy of the prior art drug ("success may be expected in three-quarters to four-fifths of cases"), states that "Even cases resistant to *shock therapy* (emphasis added) may respond" and indicates minimal well-tolerated side-effects.

5. The evidence as a whole does not establish that there was anything unobvious in *preparing* the monochlorinated iminodibenzyl starting material employed in the preparation of the claimed compound. Moreover, since a patent is sought on the compound, not the method, the method of preparation is immaterial to the issue of patentability of the compound, even if the method were novel. If the appellants had to invent a novel and unobvious method for preparing the monochloro starting material, the disclosure is inadequate to meet the requirements of 35 USC 112 since it would then be insufficient to enable one skilled in the art to prepare that starting material and there is absent a specific working example showing the preparation of the starting material.

6. The *only evidence of comparative tests*, that of Dr. Poldinger, related to comparative tests for anti-depressant activity with respect to the monochloro and dichloro compounds, does not legally establish the difference in the anti-depressant properties of the compounds urged by the appellees. This evidence was submitted on the form of an affidavit in the Patent Office. The District Court, in its oral opinion at the conclusion of the second trial, expressly stated (A-235):

If the record before this Court consisted solely of the record before the Patent Office this Court

would be inclined to sustain the decision of the Patent Office.

Hence, the comparative tests cannot be relied on to establish unobviousness for the claimed compound.

7. The affidavits of Wurz and Kunz in the Patent Office record do not constitute probative evidence in this proceeding. These affidavits were not referred to or relied on in the post-trial brief submitted after the first trial on the case. Also, there was no testimony by the affiants or competent testimony concerning these affidavits at either of the trials and therefore no opportunity for cross-examination. These essentially *ex parte* statements should be disregarded.

8. Were the affidavits of Wurz and Kunz to be considered by this Court, the showings therein are insufficient to establish the unobviousness, and therefore patentability, of the claimed compound in view of the prior art.

ARGUMENT

1. *Presumption of Validity of Patent Office Action*

In *Hays et al. v. Brenner*, 123 US App DC 96, 357 F. 2d 287, this Court stated as follows:

As to the issue of obviousness under 103, we have reiterated time and again that a presumption of validity accompanies the action of the Patent Office, and that a Court should not interfere with that action "in the absence of new evidence carrying 'thorough conviction' that has not been considered by the Patent Office". (Decisions cited).

2. *Basis For District Court's Judgment*

The District Court's oral Opinion (JA 235) expressly states that the judgment was based exclusively on new evidence adduced at the second trial (the testimony of Drs. Garrone and Deniker). According to standards laid down by this Court, this new evidence, essentially opinions and conclusions, is of little or no probative value. It cannot legally or properly be considered the sole basis for concluding that otherwise obvious subject matter—the claimed chemical compound—which is unpatentable under 35 U.S.C. 103, becomes unobvious and therefore patentable. For reasons more fully explained hereinafter, it will be shown that the District Court's reliance upon this conclusion or opinion evidence is contra to the criteria and standards set by this Court.

It is important to note that the District Court expressed agreement with the Court's original decision based upon the record made in the Patent Office and in effect with respect to the record evidence this Court desired evaluated (the evidence adduced at the first trial). With respect to the latter, the Court stated that (JA-235):

"The Court has *doubt* [emphasis added] whether that evidence, too, is sufficient to justify the conclusion of efficacy of the medicine * * *."

However, no express finding of fact relating to that evidence was made, even though this Court had expressly requested such a finding when the case was remanded. This Court in *Reynolds v. Aghnides*, 123 U.S. App. D.C. 28, 356 F.2d 367, laid down the rule that "doubt

[as to patentability] is to be resolved" not in favor of the applicant but "in favor of administrative * * * action." Thus, had the District Court complied with this Court's wishes as to findings and conclusions on that evidence, giving full effect and force to the rule of the *Reynolds v. Agnides* case, it would have had to find that such evidence was insufficient to disturb the decision of the Patent Office that claim 8 was unpatentable because of obviousness from the prior art. Having made the finding of obviousness, the District Court would then have had to conclude that claim 8 was unpatentable since obviousness of claimed subject matter creates an absolute bar, as held in *Hays et al. v. Brenner*, 123 U.S. App. D.C. 96, 357 F. 2d 287.

In concluding in the Opinion "that the plaintiffs are entitled to a patent on claim 8 of their application," the District Court expressly states that it relied upon the further evidence introduced at the second trial, namely the testimony of the two witnesses Dr. Garrone and Dr. Deniker, two professors of psychiatry, one in Geneva and the other in Paris, which the Court considered "highly impressive."

3. *The Testimony of Drs. Garrone and Deniker*

(a) *No Comparative Tests*

Apart from the fact that that testimony (JA-193 to 216) sets forth only conclusions and opinions, and therefore is of little or no probative value on the critical issue of obviousness, it must be emphasized that that testimony relates only to the use of the claimed monochloro compound and does not purport to compare that compound, as to anti-depressant properties, with the

closely related prior art compounds, namely, the dichloro compound of the Schindler et al. patent (JA-126) or the unchlorinated compound (imipramine) of the Haefliger et al. patent (JA-255) or the Kuhn publication (JA-267). Such comparative tests are believed to be required by this Court's decision in *Blanchard v. Ooms*, 80 U.S. App. D.C. 400, 153 F. 2d 651, to justify the conclusion of patentability. Mere general opinions or statements, even from experts, that the claimed compound is more effective or faster-acting or has less side effects, without the comparative test evidence upon which the opinion is based, is of no probative value on the issue of unobviousness. This Court required such comparative testing as a pre-requisite in the *Blanchard v. Ooms* case, indicating that it was a "minimum requirement". The Court of Customs and Patent Appeals in a number of its recent decisions also indicates that it is in agreement in stating that "An arguable difference is not convincing at the precise point where comparative evidence is clearly needed;" *In re Mostovych*, 52 CCPA 884, 339 F. 2d 485; *In re Shannon*, 53 CCPA 903, 356 F. 2d 548; *In re Fortess et al.*, 54 CCPA —, 152 USPQ 13.

Furthermore, if consideration be given that testimony, attention is invited to the fact that Dr. Garrone stated that the claimed monochloro compound was administered in 123 cases with "effective" results (JA-194) in about 80 percent of the cases (JA-206); that Dr. Deniker stated that he and a research group working under him had administered the claimed compound to 150 patients and that its action is "remarkable" in treating severe depressant states, apathetic schizo-

phrenia and severe neurotics, (JA-208) with about 20 percent failure (JA-215); that, in addition, at the University Clinic of Paris, the compound has been successfully used for four years with several hundred patients; and that the compound can be used in place of electric shock treatment with "an important percentage of patients" (JA-208, 209).

The general references to "effective" results, "remarkable" effects, and replacement of shock therapy in "an important percentage of cases" appear to be the evidence which the District Court considered "highly impressive." This Court has repeatedly and consistently held that results so characterized do not necessarily qualify as an advance satisfying the required standard of patentability. For example, in *Martin v. Watson*, 103 U.S. App. D.C. 106, 255 F. 2d 185, "unexpectedly good results" were held insufficient; in *Darison Corp. v. Watson*, 109 U.S. App. D.C. 296, 287 F. 2d 150, "important developments of substantial value to the industry" was not acceptable; in *Reinauer v. Ladd*, 110 U.S. App. D.C. 300, 293 F. 2d 139, "has contributed substantially by his improvement" was not effective; and in *Pollack et al. v. Ladd*, 120 U.S. App. D.C. 318, 346 F. 2d 799, the fact that results were "excellent" did not sway the Court to conclude that a patent should be granted. Accordingly, the District Court's failure to apply the criteria and standards of this Court in evaluating the evidence in the particular art constitutes reversible error. Since the evidence adduced at the second trial is the sole basis for the conclusion that the compound of claim 8 is patentable over the closely related compounds of the prior art having

the same property, it is submitted that the judgment should be reversed.

(b) *Lack of Probative Value*

Moreover, the general conclusions and opinions of the two witnesses as to the efficacy of the claimed monochloro compound, which impressed the District Court, cannot properly be considered to be of any probative value since they are not based on any primary factual evidence of record. Although the testimony that the claimed compound is an "effective" or "remarkable" anti-depressant is assertedly predicated on several hundred clinical tests, there is no primary factual evidence of those tests in the record. The best evidence would be the clinical records of the patients or of a sufficiently representative number. Such records would at least set out (for each patient) sex, age, prior medical and psychiatric history, the course of psychiatric and/or drug treatment followed including the one or more drugs administered, dosages and dates, and most importantly the clinician's personal observations prior-during-and after the course of treatment regarding efficacy as well as latency and side effects. The record is not only bare of the clinical records but does not even contain a tabulation of those records setting forth relevant factors as indicated for all the patients or for a representative number. In the absence of such primary factual evidence to support their testimony, or a reasonable approximation as by detailed tabulation, the testimony of Dr. Garrone and Dr. Deniker amounts to no more than unsupported conclusions or opinions.

Dr. Garrone's affidavit (JA-96), submitted during

prosecution of the case in the Patent Office, illustrates the need for primary factual evidence to support the conclusions of an expert witness. In that affidavit, which presents a brief statement for each of only twenty-three (23) patients treated with the claimed compound, the affiant states under "Conclusion" (JA-107):

The period of latency between the outset of the treatment and the first effect is short, usually between 4 and 6 days, a positive response manifesting itself as early as on the 2nd day of treatment.

The data in the Garrone affidavit for each patient (JA-99 to 106) includes the "Latency of effect". Examination of that data reveals the following "Latency of effect" *for the 23 patients*:

- (a) Under 6 days—9 patients
- (b) 6 days—4 patients
- (c) Over one week—7 patients
- (d) 6 days to several weeks—15 patients
- (e) Don't know—2 patients

It is difficult to see how Dr. Garrone's conclusion

The period of latency between the outset of the treatment and the first effect is short, usually between 4 and 6 days

can be justified by the overall factual latency data reported in the affidavit. It is also evident that there is no factual data to support Dr. Garrone's conclusion

a positive response manifesting itself as early as on the 2nd day of treatment.

An effort was made, during the cross-examination of Dr. Garrone (J.A.-202), to have the witness offer an explanation for the gross exaggerations stated in the "Conclusion" of his affidavit. However, appellant's counsel was prevented from proceeding on this course by the Trial Judge who twice stated that "the affidavit speaks for itself" (JA-202). The same point and its implications were further brought to the attention of the District Court in the closing argument on the case below (JA-229). It is fair to say that *Dr. Garrone's affidavit not only shows that his own unsupported testimony cannot be taken at face value—but it also demonstrates the need for factual evidence, especially primary factual evidence, to support an expert's conclusions or opinions.*

Pertinent decisions in the general law on the lack of probative value in factually unsupported expert testimony may be considered. Thus in *Balabon and Katz Corp. v. Commissioner of Internal Revenue* (CCA 7, 1929), 30 F. 2d 807, it was held that opinion evidence to be of value must be based upon admitted facts or facts within knowledge of the witness disclosed in the record; the *Balabon* case was cited for this principle of law in *Vincennes Water Supply Co. v. Public Service Commission of Indiana* (CCA Ind. 1929), 34 F. 2d 5, certiorari denied, 280 U.S. 567. In *Ramsay v. U.S.* (D.C. Mo., 1932), 55 F. 2d 333, the Court stated that one shown to be qualified as an expert, in values, may give testimony having probative value, if factual basis to support the opinion is reasonably sufficient. Also, in *W. Horace Williams Co. v. Serpas* (C.A. La.), 261 F. 2d 357, the Court held that the opinion of an expert wit-

ness is dependent on and no stronger than the facts upon which it is predicated, and it has no probative force unless the premises upon which it is based are shown to be true.

Additional authoritative publications respecting the necessity of controlled testing in the medical arts in general is called to the Court's attention. If deemed necessary, the Court could judicially notice the following statement in the authoritative work "The Pharmacological Basis of Therapeutics," edited by Goodman and Gilman (The Macmillan Company, New York, 1965), appearing on page 162 of chapter 12 (entitled "Drugs Used in the Treatment of Psychiatric Disorders," by Murray E. Jarvik):

Clinical Assessment of Pharmacotherapy. One of the most difficult problems in psychiatry is the assessment of therapy, and this is true whether the treatment is psychological, physical, or chemical. One must somehow answer the questions whether the patient is improved after treatment and whether improvement is due to the treatment. One must be particularly careful to rule out the possibility that a natural remission has occurred, or that the patient or personnel connected with the therapeutic trial have been influenced somehow by factors other than the specific treatment in question. Criteria for the evaluation of results in psychotherapy have varied from intuitive subjective generalizations of therapists or patients, through rating scales, to objective measures of behavioral change in patients.

The advent of clinical psychopharmacology in

the 1950s provided a tremendous impetus for the development of objective technics to measure behavioral pathology in large groups of patients. Drugs have the virtue over other forms of therapy that they are discrete material substances that can be measured and easily dispensed in a controlled fashion. Psychotherapy, shock therapy, or surgery could not be studied in this controlled manner. New scales and inventories to evaluate psychopathology, including those by Burdock, Wittenborn, and Lorr, were designed specifically to deal with large state-hospital populations. Modifications of the anxiety scale on the Minnesota multiphasic personality inventory (MMPI) were devised and used to evaluate drugs such as meprobamate and chlordiazepoxide; the depression scales of the MMPI have been employed to measure effects of monoamine oxidase inhibitors and imipramine, and a number of specialized depression scales have been developed.

Drugs also stimulated investigators to become more concerned about scientific methodology and the need for proper controls (see U.S. Dept. of Health, Education, and Welfare, 1962). The use of matched samples of patients receiving different drugs or placebos and of crossover designs in which the same patients were given different treatments several times according to a balanced design became feasible with pharmacological agents. Untreated controls have been used to measure spontaneous change in psychiatric status, although such patients are increasingly difficult to find.

Experimenters or subjects can intentionally or unintentionally introduce bias into an investigation by preconceived ideas of what results can be expected. This might be considered the influence of suggestion or autosuggestion, similar in most respects to that seen with hypnosis. What is commonly called the placebo response may be interpreted as the result of a preconceived idea or of the suggestion made by another individual that a particular tablet, capsule, or injection would have a particular effect. Whether high suggestibility is characteristic of a certain class of people (placebo reactors) has been a subject of some controversy. There is no question that the true pharmacological effect of drugs may be intensified or nullified by suggestion. Thus, by appropriate instructions, amphetamine has been observed to sedate patients and barbiturates to stimulate them (Ross *et al.*, 1962; Frankenhaeuser *et al.*, 1963). Raters who have been influenced to expect certain effects from drugs often find them, even when placebos have been given. In order to eliminate bias, the double-blind procedure has been widely applied to drug experiments. With this technic, both experimenter and subject are kept as ignorant as possible of the nature of the drugs being administered and someone not otherwise involved keeps the key to the drug code until the end of the experiment. Often drugs reveal their presence through strong side effects, but sometimes active placebos (i.e. those with similar side effects but no therapeutic action) may be employed to ad-

vantage. Numerous review of the placebo problem are available (*see* Wolf, 1959; Joyce, 1961).

Since suggestion can play a major role in psychotherapy, a critique of experimental design will often be included in the following discussions of the individual drugs, and descriptions of clinical effects will rely heavily on the results obtained in well-controlled rather than uncontrolled studies.

It is manifest from the above statement by Jarvik that the minimum requirements for establishing the efficacy of a drug (especially a psychiatric drug) include the use of recognized objective standard test procedures (such as the "depression [rating] scales of the MMPI" referred to by Jarvik) and the utilization of effective controls. There is no evidence that these minimum requirements were met in the tests generally alluded to by the two witnesses. Jarvik's statement that various factors may influence the effect of a psychiatric drug is borne out by "Medicinal Chemistry" (JA-274; page 88 of text; Def. Ex. 6) where it is stated with respect to imipramine:

There are a number of single factors which can influence the therapeutic response to imipramine therapy in endogenous depression: Number of phases, course of the disease, age, sex. Most clinical investigators have related the psychopathological picture to the therapeutic result. In this connection the definition of "target symptoms" coined by Freyhan (1959) has gained importance.

Moreover, in enacting the Food and Drugs statutes (Title 21, United States Code), the Congress specified

the type of evidence it considered necessary to establish the efficacy (as well as safety) of new drugs. Thus, 21 U.S.C. 355 provides, in pertinent portions, that:

(b) * * * Such person shall submit to the Secretary as part of the application (1) full reports of investigations which have been made to show whether or not such drug is safe for use and whether such drug is effective in use * * *.

(d) [An application may be disapproved where]

(5) * * * there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have * * *.
 * * * the term "substantial evidence" means evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have * * *.

Consequently, albeit in a non-patent statute, Congress expressed its sense of the evidence it considers necessary to establish the efficacy (and safety of drugs). Where, as here, efficacy of a drug is sought to be established by applicants to justify the grant of a patent, it is reasonable to presume that the standard of evidence suggested by Congress should be followed.

Clearly, the general testimony of Drs. Garrone and

Deniker does not meet the standards of evidence set out in 21 U.S.C. 355 as indicated above. It may be noted too, that probative evidence of efficacy (as is apparent from 21 U.S.C. 355) requires the submission of the raw test data (including actual clinical reports) so that the conclusion of the witnesses may be compared with the actual test results; no such data was submitted to corroborate the witnesses' testimony.

Since the appellants introduced no probative evidence of comparative tests with the prior art compounds at the second trial, and since the general testimony of efficacy—in addition to lacking probative value—does not establish patentable superiority over the prior art drugs, there is no basis for holding the claimed compound patentable in view of the entire record in the case.

4. *The Compound of Claim 8 Would Be Obvious From The Combined Teachings Of Schindler et al And The Australian Patent.*

The argument under the above heading appearing in (App. Br.-8 to 13) for former Appeal No. 19,706 is incorporated here by reference; the findings of fact there noted were made by the District Court at the conclusion of the first trial in the case; the appellee's arguments there discussed appeared in their brief in the earlier appeal.

An additional point may be made. The Australian patent does indeed disclose a large class of compounds. If so, that patent discloses a large number of compounds of closely related chemical structure (that also have closely related pharmacological properties) which

may be unsubstituted, monohalogen substituted or dihalogen substituted in the iminodibenzyl nucleus. The very sizable number of compounds comprehended by the Australian disclosure would render the claimed monochloro (monohalogen) compound obvious from the dichloro (dihalogen) compound of the Schindler et al patent.

5. The Compound of Claim 8 Is Not Patentable Over Imipramine Disclosed in The Haefliger et al Patent And The Kuhn Publication

It is not disputed by the appellees that imipramine (the unchlorinated compound), disclosed by the Haefliger et al patent (JA-255; Pl. Ex. 10) and the Kuhn publication (JA-269; Def. Ex. 4) was a well-known highly effective anti-depressant drug (Testimony of Dr. Garrone on cross-examination, JA-203) in the prior art. Imipramine has the identical chemical structural formula of the claimed monochloro compound except that it does not have the chlorine atom; the chemical structure of imipramine (in the form of its hydrochloride, i.e., HCl salt) is shown in the Kuhn publication; page 1, column 2 bottom, first formula (JA-262). It is evident that imipramine and the claimed compound are very closely related in their chemical structure. It has been established by the Court of Customs and Patent Appeals that a claimed compound is not patentable over a chemically closely related prior art compound, especially in the absence of convincing and probative evidence demonstrating a completely unexpected result.

In re Riden et al, 50 CCPA 1411, 318 F. 2d 761;

In re Herr, 50 CCPA 705, 304 F. 2d 907;

In re Druey et al, 50 CCPA 1538, 319 F. 2d 237;

In re Zickendraht et al, 50 CCPA 1529, 319 F. 2d 225;

In re Lohr et al, 50 CCPA 1274, 317 F. 2d 388;

In re Surrey et al, 50 CCPA 1336, 319 F. 2d 233.

The oral opinion of the District Court indicates that the Court was impressed by the testimony of Dr. Garrone and Dr. Deniker as to the "superior efficacy of the applicant's compound" (JA-238), that "it is being regularly used and even to the extent of supplanting electric shock treatment" (JA-238), and that it exhibits "less side effects than is expected or caused by other compounds at times and that such side effects as occasionally existed were not dangerous" (JA-236). Dr. Garrone also testified that the claimed compound acts twice as fast as imipramine and requires about half the dosage (JA-196).

As indicated hereinabove, the testimony of the two witnesses concerning the alleged superior qualities of the claimed compound vis-a-vis imipramine has no probative value since it is not supported by primary factual evidence, there also being no factual evidence of comparative tests with the two compounds. The absence of comparative test cannot be explained away by asserting that imipramine was not relied upon by appellant until just prior to the second trial since the evidence (Haeffiger et al, JA-255; Kuhn, JA-263; and "Medicinal Chemistry", JA-273) shows that imipramine, so closely related in chemical structure, was a well-known and effective anti-depressant; this is fully corroborated by the testimony of the two witnesses.

Furthermore the Kuhn publication expressly states (JA-267):

even cases resistant to *shock therapy* (emphasis added) may respond to imipramine.

Thus, Kuhn not only states that imipramine may be effective where shock therapy is not—but logically implies that imipramine is capable of being substituted for shock therapy in many if not most cases. The appellees assert no more for their compound—and that they have not proven by probative evidence.

In addition, Dr. Deniker testified that the claimed compound is effective in cases of severe depression, apathetic schizophrenia and group neurotics (JA-208). Kuhn (JA-267) and "Medicinal Chemistry" (JA-233) clearly show that imipramine is also highly effective with such patients. It is noted, for example, that Kuhn states (JA-267):

In Schizophrenia without excitement, however, it (imipramine) may work well.

Dr. Garrone testified that the side effects with the claimed compound "could be dryness of the mouth, breaking out in sweat, difficulty of accommodation, sometimes cases of dizziness" (JA-206). Both Kuhn (JA-267) and "Medicinal Chemistry" (JA-275) specify similar side effects for imipramine and indicate that the side effects are minimal and not dangerous.

6. *Matter of Preparing The Claimed Compound*

The argument under the above heading appearing in (App. Br.-13 to 18) for Appeal No. 19,706 is incorporated here by reference; there also the appellees'

arguments discussed appeared in their brief for the earlier appeal and the findings of fact noted were made by the District Court at the end of the first trial in the case.

7. Properties of the Compounds

The statement and arguments under the above heading appearing in (App. Br.-18 to 28) for Appeal No. 19,706—with the exception of the argument under subheading (a)—are incorporated here by reference; appellees' argument there discussed also appeared in their brief in the prior appeal and the findings of fact noted were made at the termination of the first trial. With respect to the Garrone affidavit under subheading (c), the remarks in the prior brief are relevant except that Garrone did appear as a witness at the second trial—and the Garrone affidavit and testimony have been further fully considered in the present brief.

CONCLUSION

It is respectfully submitted that the District Court erred as a matter of law in concluding that the appellees are entitled to receive a patent containing claim 8 in their application on the sole basis of the non-probative testimony of Drs. Garrone and Deniker and for the other reasons discussed herein.

Respectfully submitted,

JOSEPH SCHIMMEL,
Solicitor, United States Patent Office.

JACK E. ARMORE,
Of Counsel.

BRIEF FOR APPELLEES

IN THE
United States Court of Appeals
For the District of Columbia Circuit

COMMISSIONER OF PATENTS,

Appellant,

v.

WALTER SCHINDLER and HENRI DIETRICH,
Appellees.

No. 21,309

ON APPEAL FROM A JUDGMENT OF THE UNITED STATES
DISTRICT COURT FOR THE DISTRICT OF COLUMBIA

WILLIAM A. SMITH, JR.
Woodward Building
15th and H Streets, N.W.
Washington, D. C. 20005
Attorney for Appellees

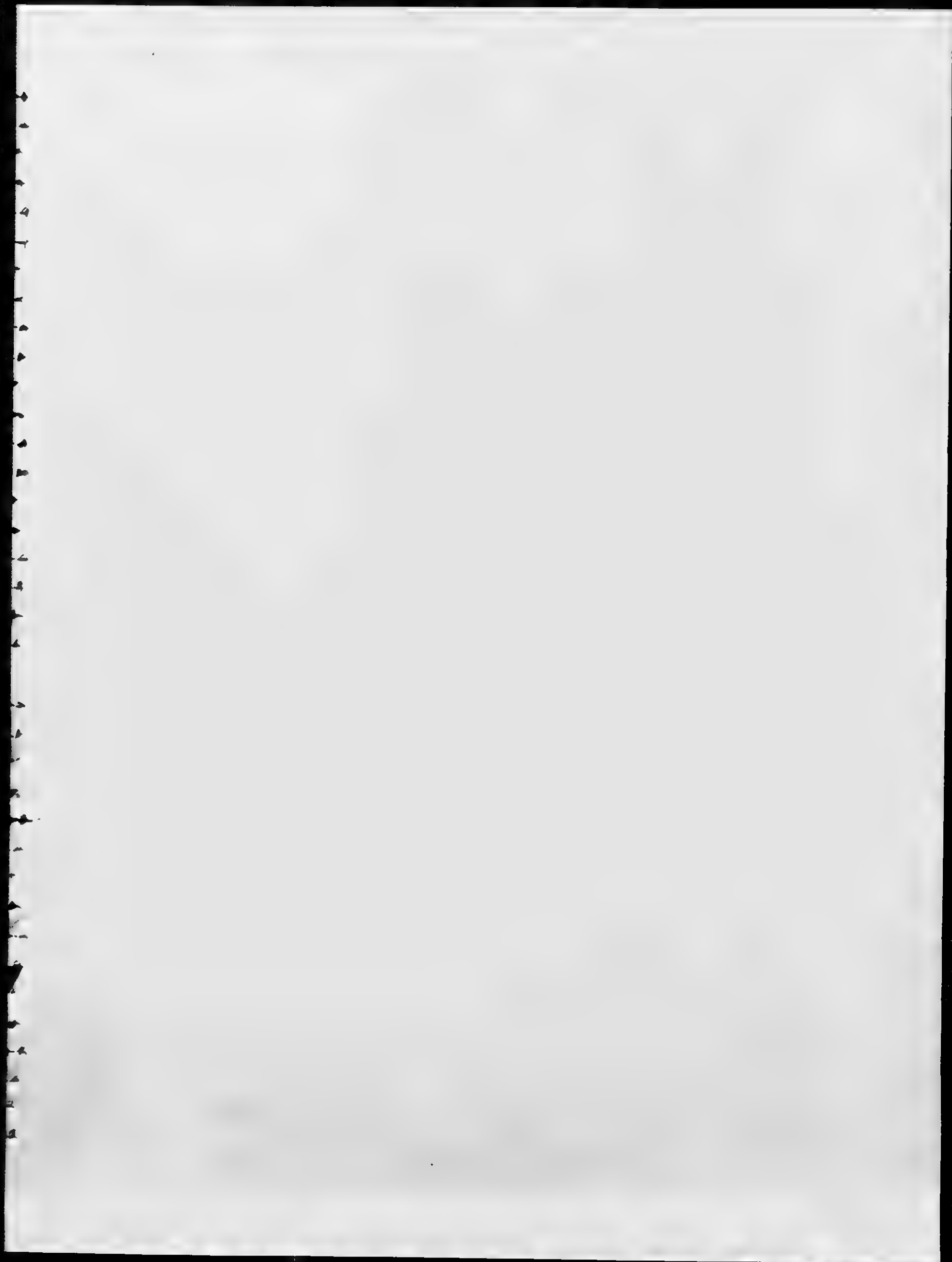
CASPAR C. SCHNEIDER, JR.
DAVIS, HOKIE, FAITHFULL & HARGOOD
30 Broad Street
New York, New York

KARL F. JORDA
Ardsley, New York
Of Counsel

United States Court of Appeals
for the District of Columbia Circuit

FILED JAN 5 1968

Nathan J. Paulson
CLERK



Appellees' Statement of Questions Presented

In Appellees' view, the questions presented on this Appeal, which arises out of a suit against Appellant, the Commissioner of Patents, to authorize him to issue a patent on a new chemical compound, are:

1. Was it error for the District Court to give credence to testimony relating to the efficacy of the claimed compound in the treatment of mental depression by a physician and professor of neuropsychiatry who had conducted a systematic study of the effectiveness of the compound on 150 patients and was generally familiar with its regular use on hundreds of other patients, because the clinical records on which that testimony was based were not in evidence?

2. Was it error for the District Court to give credence to testimony from two physicians on the relative efficacy of the claimed compound and a known prior art compound, in the treatment of depression, where that testimony was based on experience with the two compounds but not on a formal series of comparative tests?

3. Where the record shows the claimed compound to be effective as a medicine in the treatment of mental depression at half the dose and in half the time as the nearest prior art medicine, and to be capable of replacing electro-shock treatment, was the District Court's finding that the efficacy of the claimed compound was so large and far reaching as to amount to a new result, clearly erroneous?

4. Does the Record, taken as a whole, show the District Court's finding that the claimed compound was not obvious from the prior art, to be erroneous?

BRIEF FOR APPELLEES

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For the District of Columbia Circuit

COMMISSIONER OF PATENTS,

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WALTER SCHINDLER and HENRI DIETRICH,

Appellees.

No. 21,309

ON APPEAL FROM A JUDGMENT OF THE UNITED STATES
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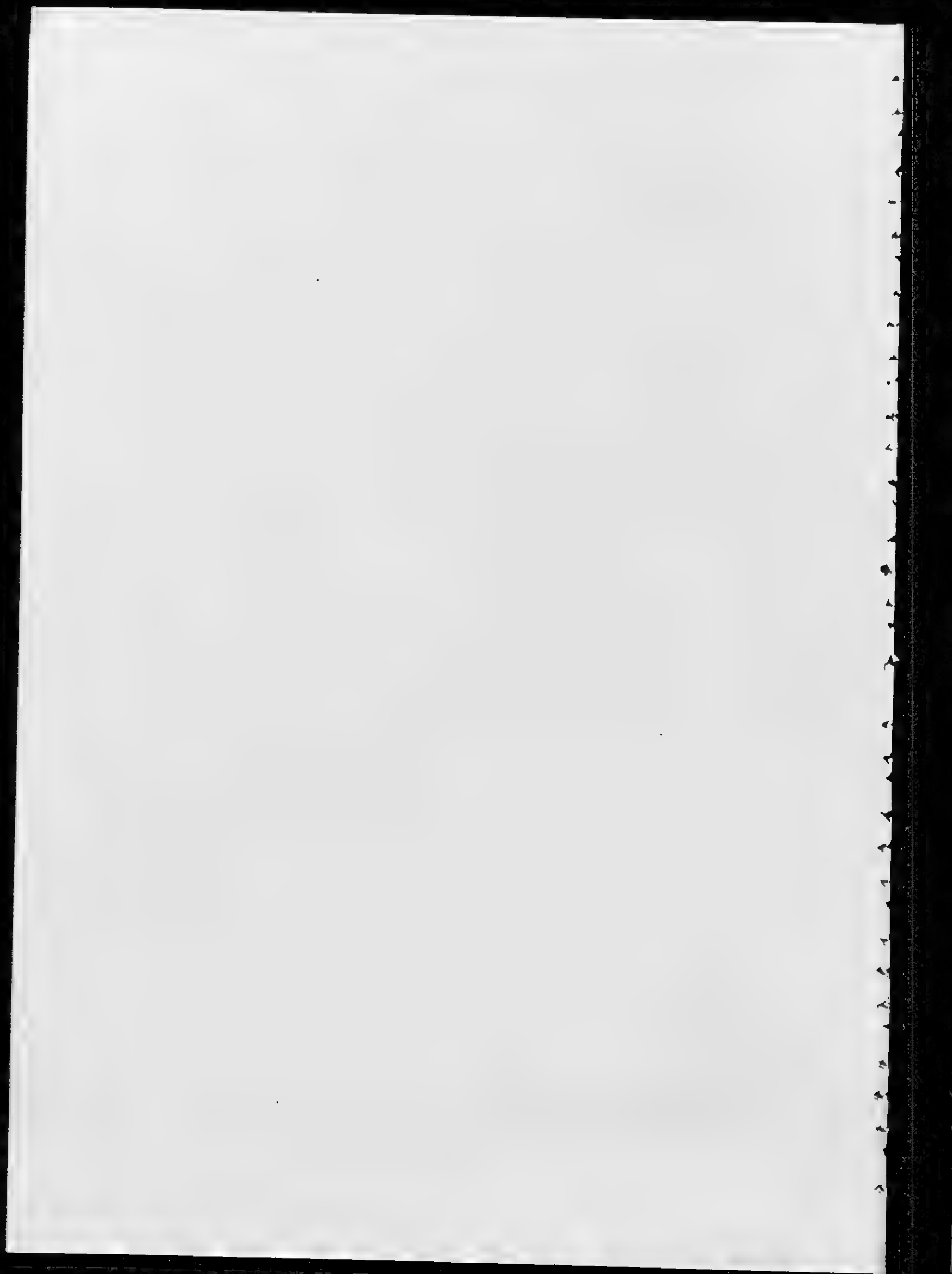
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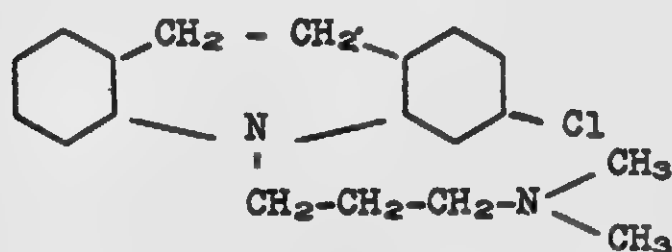
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Counter-Statement of the Case

The single patent claim presented on this appeal, claim 8 of Appellees' patent application, Serial No. 857,274, filed December 4, 1959, is to the compound 3-chloro-5-(γ -dimethylamino-propyl)-imino-dibenzyl. This compound is useful as a medicine in the treatment of mental depression. It has the following structural formula:

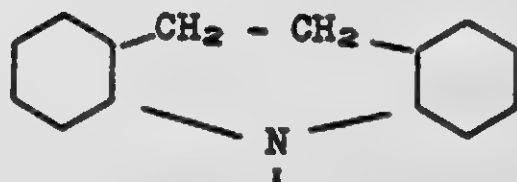


FORMULA I

It is conventionally called chlorimipramine. In the present record it is sometimes referred to as monochlorimipramine, the monochloro compound, or the one-chlorine compound.

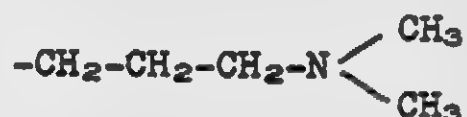
It is convenient to discuss the structure of chlorimipramine in terms of three constituent parts. These are:

First, a central core or nucleus, often referred to as an "iminodibenzyl nucleus":



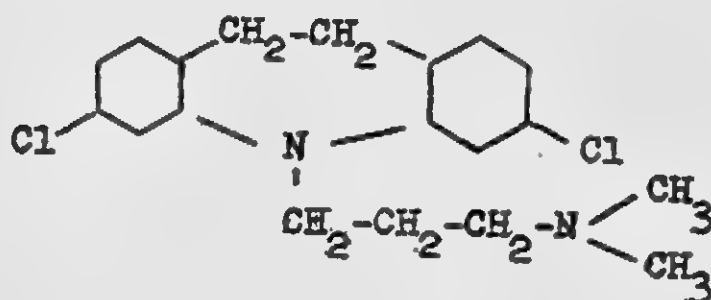
Second, a single chlorine atom, represented by the symbol Cl. In the compound in question this is attached at the lower righthand corner of the "iminodibenzyl nucleus".

Third, a tail, connected to the nitrogen atom ("N") of the nucleus and having the formula:



The Patent Office rejected claim 8 as obvious over two prior patents, Schindler et al. U. S. Patent No. 2,813,857 (JA 126) and Australian Patent No. 215,335 (JA 128).

The Schindler patent discloses the specific compound 3, 7-dichloro-5-(γ -dimethylamino-propyl)-imino-dibenzyl, which has the formula:



FORMULA II

A comparison of this formula with Formula I shows that the claimed compound has only one chlorine atom, while the patented compound has two chlorine atoms, symmetrically positioned on the nucleus. It is sometimes referred to as the dichloro or the two-chlorine compound. The Schindler et al. patent says that its compounds can be used, among other things, for the treatment of mental disorders. However, it does not mention mental depression, as such, and the record (JA 68) shows that in fact the compound is useless for treating depression.

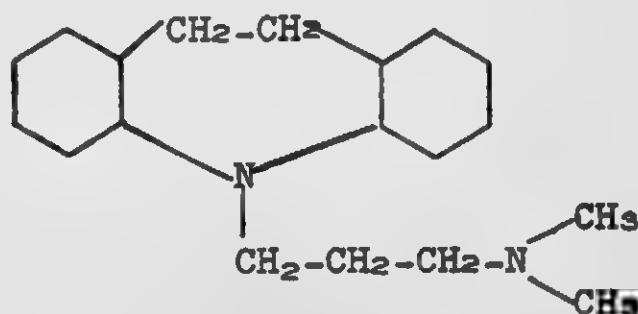
sioner under 35 USC 145. At a trial held in February 1965, sometimes referred to as the first trial, evidence was introduced in addition to that presented in the Patent Office and including further evidence of anti-depressant properties.

The District Court, in a decision dated June 23, 1965 (JA 140), held that it could not consider the evidence of anti-depressant properties because such properties were not disclosed in the text of the patent application. It therefore held the claim unpatentable.

Appellees then appealed to this Court (Appeal 19,706). This Court found that the specification *was* adequate to support a proffer of evidence of anti-depressant properties, and remanded the case to the District Court to consider the evidence already presented, together with such additional evidence as it might wish to accept, to make new findings, and to return the case to this Court.

In accordance with this Court's mandate, a second trial was held January 11, 1967. On January 5, 1967, just six days before the trial, Appellant informed Appellees that he proposed to rely on two new prior art references, Haefliger U. S. Patent No. 2,554,736 (JA 255) and an article by Kuhn in *Schweizerische Medizinische Wochenschrift* (1957) (JA 262).

Both of these latter references deal with a compound known as imipramine, a known anti-depressant, whose formula is



FORMULA IV

A comparison of Formula I and Formula IV shows that the structural difference between the compound claimed and imipramine is that the latter has no chlorine at all.*

At the second trial, Appellees presented three witnesses.

Dr. Daniel Prins, a chemist, testified to the effect that the Australian patent disclosure includes some six billion different compounds (JA 161); that the most obvious compounds resulting from combining the Australian patent with the Schindler et al. or Haefliger patents would be compounds having the peculiar tail of the Australian compounds (JA 162, 190-191): that none of these compounds showed any indication of anti-depressant activity (JA 162, 190-191).

Dr. Gaston Garonne, a psychiatrist and professor at the University of Geneva, Switzerland, testified that he had used the compound of claim 8 on about 123 patients (JA 194). He confirmed the results set out in his affidavit made of record in the Patent Office, as to the efficacy of the compound in the treatment of depression (JA 195). He stated that he was familiar with the prior art compound imipramine and that chlorimipramine acts much faster (JA 196), is effective at about one-half the dosage required for imipramine (JA 196) and has considerably less side effects (JA 196). He said that chlorimipramine can be used to treat severely depressed patients who would otherwise require hospitalization and that in such cases imipramine could not be used (JA 196, 197).

* Appellant's Brief (p. 22) refers to the Kuhn article as showing the HCl salt of imipramine. Imipramine, chlorimipramine and many, many other materials are often made in the form of their acid salts, of which the HCl salt is the most usual, for ease of handling, identification and administration. The chlorine in the HCl moiety plays no more role in the physiological action of any of these compounds than does the gelatin or sugar coating of a capsule or pill in the action of the medicine that the pill or capsule contains. In any case, claim 8 is directed to the basic compound, Formula I, rather than the salts.

Professor Pierre Deniker, a physician and professor of Neuropsychiatry at the University of Paris, testified that chlorimipramine had been used on several hundred patients at the University clinic with remarkable results (JA 208). He further indicated that his research group had conducted a systematic study of some 150 patients (JA 207-208) and had established that in cases of severe depression, chlorimipramine had been found capable of replacing electro-shock treatment (ECT) (JA 208, 209, 214). Professor Deniker further stated that he was familiar with imipramine and that in his judgment it was not suitable as a substitute for ECT (JA 210). He stated that to use any compound other than chlorimipramine as a replacement for ECT with severely depressed patients would involve a grave risk of suicide (JA 209).

The trial court, at the conclusion of the second trial, found that chlorimipramine was being used on a very substantial scale in the treatment of mental depression with a very high degree of success; that while other compounds such as imipramine, had been used to treat depression, chlorimipramine was far superior, its efficacy being so large and far reaching as to amount to a new result (JA 248-249). It therefore concluded that chlorimipramine was unobvious over the prior art cited by the Appellant (JA 249) and entered a judgment for plaintiffs-appellees (JA 250-251).

It is from this judgment that the present appeal is taken.

Summary of Argument

1. While the ultimate question of obviousness is a question of law rather than fact, the findings of the District Court that the superiority of the claimed compound as an anti-depressant is so large and far reaching as to amount to a new result is a finding of fact and as such, under Rule 52(a) FRCP, must be presumed valid unless "clearly

erroneous". No clear error has been shown, and since obtaining a new result supports a conclusion of unobviousness, the District Court's decision in favor of plaintiffs-appellees was proper, and the appeal should be dismissed.

2. Appellant's brief asserts two grounds of unpatentability, viz;

(a) The compound is obvious from Schindler et al. and the Australian patent.

(b) The compound is obvious from the Haefliger patent and the Kuhn article.

As to the first ground, the Schindler patent discloses a compound having two chlorine atoms symmetrically positioned on the molecule. The claimed compound has only one chlorine atom. This difference in structure means that the claimed compound cannot be made by the processes normally employed for making the Schindler et al. two-chlorine compound. Moreover, the properties as well as the structure of a new compound must be considered on the issue of obviousness and the two-chlorine compound is useless as an anti-depressant, whereas the claimed compound is remarkable in its anti-depressant properties.

The Australian patent does not suggest modifying the two-chlorine compound of Schindler to make the claimed compound. While the Australian patent is broad enough to embrace compounds having one chlorine atom on the iminodibenzyl nucleus, this is only one possible variant in a disclosure of several billion compounds. There is no particular preference for compounds containing one chlorine atom. Moreover, all the compounds in the Australian patent must have a piperazine group in the tail. If such a tail is put on an iminodibenzyl nucleus with two chlorine atoms (as in the Schindler patent), with one chlorine atom (as in the claimed compound), or with no chlorine atoms (as in the Haefliger and Kuhn references),

the result is a compound with no anti-depressant properties.

As to the rejection on Haefliger and Kuhn, the compound imipramine disclosed therein contains no chlorine on the iminodibenzyl nucleus.

There is no suggestion in Kuhn or Haefliger of attaching chlorine or any other group or atom on the nucleus, much less attaching a single chlorine atom in the precise position that the chlorine atom occupies in the claimed compound. As the Australian patent shows, an iminodibenzyl nucleus can be modified in any of a number of different ways—some 40,000 different modifications of the nucleus are disclosed in the Australian patent alone. It lacks reality to say that the particular and specific modification here claimed was obvious from Kuhn and Haefliger.

Imipramine, the compound of Kuhn and Haefliger, is an anti-depressant. However, the claimed compound is—

- (a) effective at half the dose
- (b) effective in half the time
- (c) has less side effects; and
- (d) unlike the Haefliger compound, can be used in place of electro-shock treatment in severe depressions.

On this basis, the trial court properly found the efficacy of the new compound to be so much greater as to amount to a new result. We add that if the properties of the Schindler patent compound, containing two chlorine atoms, are considered with the properties of the Haefliger and Kuhn compound, containing no chlorine, the conclusion is that chlorine in the molecule suppresses anti-depressant activity. Certainly the great *increase* in efficacy which is obtained with the claimed compound was not obvious.

3. Appellant's attack on the District Court's findings is unjustified. The Court's Findings were based on the entire Record, and not exclusively on the testimony at the second trial. The testimony of Drs. Garonne and Deniker, while involving professional judgment, was of a factual nature and not merely opinions and conclusions. In any case, however, the basis for their testimony was clearly stated beforehand. The assertion that additional raw clinical data was required to be put into the record is unwarranted. The Garonne testimony and the Pöldinger testimony (at the first trial) were supported by data given in affidavits of record in the Patent Office. While the absence of raw data might affect the weight to be accorded the Deniker testimony, it was clearly within the province of the District Court to credit that testimony.

So far as formal comparative tests are concerned, the two-chlorine compound of the Schindler patent was tested against the claimed compound by the witnesses Sigg and Pöldinger, among others, and the results are in the record (JA 53-56, 61-68, 94). So far as imipramine, the no-chlorine compound of Kuhn and Haefliger is concerned, elaborate tests cannot reasonably have been expected when Appellees had only six days' notice of the intention to rely on this prior art. Both Drs. Garonne and Deniker were familiar with the two compounds and testified to the superiority of the claimed compound. It was not clearly erroneous for the District Court to have believed that testimony. There is no basis in statute or precedent for requiring experimental data of the kind required by the Food and Drug Administration for New Drug Approval to be furnished in connection with a patent application. For the Commissioner to require such showing in this particular case, without first establishing a definitive Rule or Regulation, would be completely and objectionably arbitrary. In any case, however, the ultimate nature of the investigation about which testimony was given was in general accord with the requirements of the FDA.

ARGUMENT

I. The Holding of the District Court That the Claimed Compound Was Unobvious Over the Prior Art of Record Should Not Be Set Aside Unless Clearly Erroneous.

Rule 52(a), Federal Rules of Civil Procedure, requires that in actions tried without a jury—

“Findings of fact shall not be set aside unless clearly erroneous, and due regard shall be given to the opportunity of the trial court to judge of the credibility of the witnesses.”

In Finding of Fact 11 (JA 249) the District Court found the claimed compound to be unobvious over the prior art relied upon by Appellant. Subsequently, this Court in *Higley v. Brenner* — App. D. C. —, — F. 2d —, 155 USPQ 481 (1967), following the concurring opinion in *Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp.*, 340 U. S. 147, 155-6 (1950), has held that obviousness is a question of law. The presumption of correctness mandated by Rule 52(a) therefore is not directly applicable to Finding 11. That ultimate Finding, however, was drawn from Findings of Fact 8 to 10, inclusive, as follows (JA 248-249):

“8. The record, particularly the testimony of Dr. Gaston Garonne and Professor Pierre Deniker, shows that the compound in question has been used and is being used on a very substantial scale in the treatment of mental depression, with a very high degree of success.

9. Other compounds, such as that disclosed in Patent No. 2,554,736 and the Kuhn article, have been used to treat depression, but the compound claimed is so far superior to those compounds that it can be used

to supplant electro-shock treatment in severe depressions, a faculty not possessed by the prior art compounds.

10. The efficacy of the claimed compound as a medicine in treating depression, compared to that of the prior art compounds, is so large and far reaching as to amount to a new result."

These Findings of Fact are entitled to the presumption of correctness of Rule 52(a) and ought not to be overturned unless "clearly erroneous".

But if an inventor obtains "a new result, an unobvious result, an unexpected result, a far more efficient result, or a more economical result," his invention satisfies the requirements of patentability. *Higley v. Brenner, supra*; *Aerosol Research Co. v. Scovill Mfg. Co.*, 334 F. 2d 751, 141 USPQ 758, 7 Cir. (1964); *Copease Mfg. Co. v. American Photocopy Equipment Co.*, 298 F. 2d 772, 781, 132 USPQ 87, 95, 7 Cir. (1961).

Thus it necessarily follows that if Appellees obtained a new result, as the District Court has found to be the case, their invention was unobvious and patentable. Hence, the presumption of correctness which in this case attaches to the District Court's finding of a new result amounts to a presumption that the finding of unobviousness is correct and should not be set aside unless clearly erroneous.

The Appellant's attack on the District Court's findings is, in the last analysis, an attack on the credibility of the witnesses. The District Court was, of course, peculiarly suited to judge whether or not the witnesses were to be believed, and the Appellant's attack falls far short of showing the clear error which would be required to set aside the holding of the District Court.

II. The Claimed Compound Is Not Obvious From the Schindler Patent Alone or Taken With the Australian Patent.

Appellant has specified two grounds for holding the claimed compound unpatentable. The first is that it would be obvious from the prior patent to Schindler et al. 2,813,857 (JA 127) in view of Australian patent 215,335. This is clearly untenable.

A. The Claimed Compound Is Structurally Distinct From the Compounds Disclosed in the Schindler et al. Patent.

While Schindler et al. 2,813,857 (JA 127) discloses a compound, Formula II, above, which resembles the compound of claim 8, it is different from the compound of claim 8, in that it has two chlorine atoms on the iminodibenzyl nucleus, whereas the compound of claim 8 has only one chlorine atom.

B. The Compound of Claim 8 Cannot Be Made By the Normal Method Used to Make the Compound of the Schindler et al. Patent.

Among the reasons why the claimed compound is not obvious from the Schindler et al. patent is that it cannot be made by the methods normally used to make the compound of that patent. The reasons for this are discussed at some length in our Main Brief (pp. 21-23) and Reply Brief (pp. 10-11) in Appeal 19,706, to which the Court is respectfully referred. To put them in simplest form, in the Schindler et al. patented compound (Formula II), the chlorinated nucleus of the molecule is symmetrical, with a chlorine atom attached to both sides. It can therefore be made by joining two identical components. In the claimed compound (Formula I), on the other hand, the chlorinated nucleus is unsymmetrical, since it has a chlorine atom on only one side. All efforts to make the nucleus

by joining two dissimilar components in the manner used to make the symmetrical nucleus, were fruitless. Appellees were required to put together a new combination of known process steps to arrive at the claimed compound.

Of course we are not here concerned with the patentability of a process, but rather with whether the compound of claim 8 would be obvious. On this question, however, the fact that the compound claimed cannot be made by the normal methods used to make the prior art compounds is pertinent, and emphasizes the unobviousness of the compound.

In *In re Schecter and La Forge*, 40 CCPA 1009, 205 F 2d 185, 98 USPQ 144 (1953), the Court of Customs and Patent Appeals, in considering the patentability of compound claims, observed (USPQ p. 150):

"The sole reference La Forge et al. does not disclose or even suggest any process for synthesizing even the cyclopentenolone scission products disclosed therein, let alone the new cyclopentenolones disclosed herein. The preparation of the cyclopentenolones here claimed required the discovery and development of a complex process of synthesis, and a new class of patentable hydroxydiketones for starting materials."

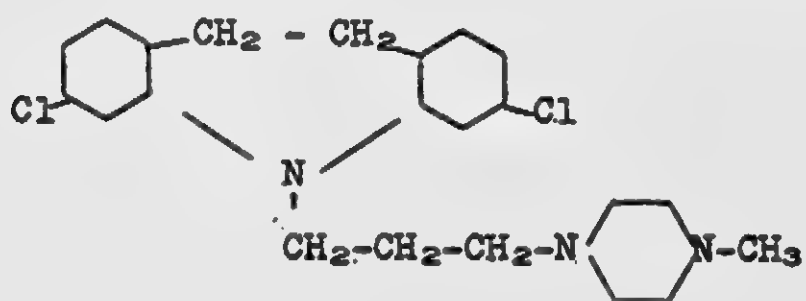
C. The Compounds of the Australian Patent Are Essentially Different From Those Now Claimed.

The compounds of the Australian patent (Formula III, *supra*) all contain a piperazine ring, which is the group:



Neither this group, nor any group having a remotely similar configuration, is present in the compound of claim 8.

Dr. Murray Weiner testified (JA 35, 36) that the compound of the Australian patent which is probably closest to the compound disclosed in the Schindler patent, namely



proved to be so toxic in animal studies that it could not be tested on humans. The fact that this compound had no therapeutic properties was confirmed by Dr. Prins (JA 163). Dr. Prins also noted (JA 164, 191) that similar compounds having the Australian tail with one chlorine atom in the nucleus (PX 9-JA 254) and no chlorine in the nucleus (PX 14-JA 261)* had no anti-depressant properties.

D. The Australian Patent Cannot Properly Be Combined With the Schindler et al. Patent to Render the Compound of Claim 8 Obvious.

In the Australian patent the symbols Y and Y₁ (Formula III, *supra*):

“... are the same or different and are selected from hydrogen atoms, halogen atoms and lower alkyl, lower alkoxy, aryl and aryloxy groups ...”

Since chlorine is a halogen, the formula embraces compounds having an iminodibenzyl nucleus bearing one chlorine atom, as well as compounds having two chlorine

* The material appearing on page 261 of the joint appendix is plaintiff's exhibit 14. The material on page 260 is plaintiff's exhibit 13B.

atoms. The Patent Office position has been that because the Australian formula is broad enough to embrace both monochloro and dichloro compounds, it suggests modifying the dichloro compound of Schindler et al., to give the monochloro compound of claim 8.

This position disregards three important facts. The first is that the Australian disclosure embraces not only mono and dichloro compounds, but compounds with either one or two fluorine, bromine, iodine, methyl, ethyl, propyl, butyl, methoxy, ethoxy, propoxy, butoxy, pentoxy, phenyl, naphthyl or phenoxy groups on the nucleus, in any of four different positions, as well as no substituents at all on the nucleus. This, of course, only indicates the number of compounds available by varying Y and Y₁. When the other variable elements in the formula are considered, some six billion compounds are embraced within the formula (JA 161). To select from these billions of variations the monochloro variation and then import it into the Schindler et al. compound to get a useful anti-depressant therapeutic is itself a discovery of patentable distinction (*E. I. DuPont de Nemours v. Ladd*, 117 App. D. C. 246, 328 F 2d 547, 140 USPQ 297 [1964]).

The second factor militating against the Patent Office position is that nowhere in the Australian patent is there any teaching of how a monochloro substituted compound can be made. The procedures disclosed in the patent describe only means for tacking a tail on the iminodibenzyl nucleus. But as we have pointed out above, and as Dr. Prins and Dr. Rubin testified, at the time of the present invention the procedures necessary for making a monochloro iminodibenzyl were unknown (JA 19, 42, 43).

Finally, the Schindler et al. patent requires a dichloro substituted compound. The Australian patent embraces a dichloro substituted compound every bit as much as it embraces a monochloro substituted compound, and requires a piperazine tail. The obvious result of adding the Aus-

tralian teaching to the Schindler et al. teaching is therefore to add a piperazine containing tail to the dichloro nucleus of Schindler et al. But when this is done, as indicated by Dr. Weiner and Dr. Prins (JA 35, 36, 163), the result is a useless compound, so toxic it cannot be tested on humans.

Modifying the Schindler et al. patent according to the Australian patent to give the claimed compound would be obvious only after reading appellees' application.

E. The Properties as Well as the Structure of A Compound Must Be Considered in Determining Patentability.

The cited proposition is now believed to be firmly established by decisions of this court (*E. I. DuPont de Nemours v. Ladd* (*supra*)); and the Court of Customs and Patent Appeals. (*In re Lambooy*, 49 CCPA 985, 300 F 2d 950, 133 USPQ 270 (CCPA 1962); *In re Petering and Fall*, 49 CCPA 993, 301 F 2d 676, 133 USPQ 275 (CCPA 1962); *In re Papesch*, 50 CCPA 1084, 315 F 2d 381, 137 USPQ 43 [CCPA 1963]).

F. The Properties of the Claimed Compound Are Quite Different From Those of the Compound Disclosed in the Schindler et al. Patent or the Closest Compounds of the Australian Patent.

In the Patent Office and at trial, Appellees offered substantial proofs to bring out the difference in properties between their claimed compound on the one hand, and the compounds of Schindler et al., or the Australian patent, on the other.

Affidavit A by Dr. Heinrich Wirz (JA 88) compared the spasmolytic properties and the serotonin antagonism of the compound of claim 8 with that of two compounds having a single chlorine atom in the iminodibenzyl nucleus and a piperazine group (such as required by the Aus-

tralian patent) in the tail. The compound of claim 8 showed a spasmolytic action over $3\frac{1}{2}$ times greater than one of these compounds and over seven times greater than the other. As to serotonin antagonism, the compound of claim 8 was about 8 times as effective as one piperazine compound and over $4\frac{1}{2}$ times as effective as the other.

Affidavit B by Dr. Wirz (JA 90) compares, *inter alia*, spasmolytic and serotonin antagonistic properties of the claimed compound with the compound of Schindler et al. It is shown that the compound claimed is about $6\frac{1}{2}$ times as effective spasmolytically as the Schindler et al. prior art compound. As to serotonin antagonism, the claimed compound is highly effective at low concentrations where the prior art compound has little or no effect. Even at higher concentrations, the prior art compound is only about $\frac{3}{5}$ as effective as the claimed compound.

The affidavit of Dr. Heinrich Kunz, of the University of Zurich, Switzerland (JA 109) shows that the differences in spasmolytic action between the claimed compound and the compound of Schindler et al. are differences in kind, not merely of degree.*

At the first trial, Dr. Ernest Sigg testified to the fact that the compound of claim 8 had strong reserpine antagonistic properties, while the prior art compound was lacking in those properties (JA 54-56). Reserpine antagonism is indicative of antidepressant activity. Dr. Sigg also in the compound of Schindler et al. are differences in kind, between the two compounds (JA 59-60).

* Appellant has objected (Brief p. 8) to the Wirz and Kunz affidavits because they were not referred to in the post-trial Brief after the first trial and because the affiants were not called upon to testify. However, the Patent Office record is properly part of the present record (*General Electric Co. v. Hygrade Sylvania Corp.*, 61 F. Supp. 476, 61 USPQ 263, 288, D. C. SD N. Y. [1944]), and was introduced without objection. The lack of opportunity for cross-examination may affect the weight of this evidence, but it is competent evidence which may be considered.

The tests referred to above were laboratory tests performed *in vitro* or on animals. The most striking property demonstrated, however, is the effect of the claimed compound in treating mental depression in human beings.

The Court may take judicial notice of the interest prevailing throughout this country and indeed the world in the treatment of mental disorders. The intricacy and complexity of man's physical system is exceeded only by the complexity of the mind and spirit. To predict, on a rational basis, the effect a particular chemical compound will have on these entities is simply not possible within the limits of present knowledge. This is brought out in various parts of the record; for example, Dr. Weiner (JA 36) cited one case in which a change in the position of the tail on the iminodibenzyl nucleus turned a compound from a tranquilizer into an anti-depressant having no tranquilizing properties. Dr. Prins (JA 176, 259, 260) cited a number of specific instances where small changes in structure gave great changes, at times reversals, of physiological effects. And as Dr. Rubin pointed out (JA 51), one does not normally expect compounds having similar molecular structures to have similar *biochemical* or *physiological* properties. Much less could one predict the effect of variations in chemical structure on *mental* or *psychological* behavior.

The evidence presented in the record of the effect of the compound of claim 8 compared to the dichloro compound of the Schindler et al. patent in the treatment of mental depression is therefore particularly interesting.

The affidavit of Dr. Walter Pöldinger (JA 95), a psychiatrist and chief of the psychopharmacological department of the cantonal (state) psychiatric clinic at St. Urban, Lucerne, Switzerland, gives an account of clinical tests on ten patients suffering with endogenous depression and sixteen with schizophrenia who were treated with the dichloro compound of the Schindler et al. patent. These patients showed either no change during the period of

treatment or grew worse. These results were then compared with the effect of the monochloro compound of claim 8 on four patients suffering with endogenous depression and three with schizophrenia. The effect on the drive or mood of the patients was from moderately to much improved. Dr. Pöldinger further testified at the trial (JA 66), as to these tests:

"Q. In summary, what is the significance of the tests reported here from the standpoint, for example, of the identity, or the lack of identity, or the significant difference or lack of significant difference between the test compounds? A. We have found a significance because the dichloro compound has had no effect and the monochloro compound has had a very strong effect on depressive states."

As pointed out by Dr. Pöldinger at the trial (JA 66-67), other work than that reported in the affidavit was carried on with the compound of claim 8.

"Q. Was any other work done with the dichloro compound, as far as you know? A. With the dichloro it was not possible because it was necessary to stop the investigations. With the monochloro I have later on made other investigations but I have not published them.

Q. And in all these other investigations, what were the results with respect to the monochloro? A. The same as I have written in this affidavit.

Q. In other words, you got the same results? A. I got the same results with more patients later on.

Q. And what are those results? A. A good stimulating effect in depressive states."

The affidavit (JA 96-107) and testimony (JA 193-206) of Dr. Gaston Garonne, psychiatrist in charge of the Psychiatric Polyclinic at the University of Geneva, Switzerland, and the testimony of Prof. Pierre Deniker of the

University of Paris, France, discussed more extensively below, are further evidence of the outstanding nature of the claimed compound as an anti-depressant.

To summarize, so far as the combination of the Schindler and Australian patents are concerned, there is no suggestion of the claimed compound any more than of any of a very large number of other compounds. The closest compound disclosed in the Schindler et al. patent does not have anti-depressant properties. And the most logical compound obtained by modifying Schindler in accordance with the Australian patent is too toxic to test on humans.

Under the circumstances, the claimed compound with its characteristic anti-depressant properties was not obvious from the prior Schindler et al. and Australian patents.

III. The Claimed Compound Is Not Rendered Obvious By the Kuhn Article or the Haefliger Patent.

Appellant has also asserted that the claimed compound is obvious over the Haefliger patent and the Kuhn article.

These references are concerned with the compound imipramine, Formula IV above.

Imipramine, as we have seen, contains no chlorine on the nucleus, and there is no suggestion in either Haefliger or Kuhn which would lead one to modify imipramine by adding chlorine to the nucleus. The number of possible modifications of imipramine is very great. All of the compounds of the Australian patent are possible imipramine modifications, and as Dr. Prins pointed out (JA 159-161), the Australian patent discloses around 40,000 different variations of the iminodibenzyl nucleus alone; and some 6,000,000,000 variants overall. There is absolutely nothing in Haefliger or Kuhn which would render obvious the partic-

ular variant now claimed, with a single chlorine atom in a single specific position on the nucleus.

It is clear that the claimed compound cannot be made by the methods used to make imipramine, because it is necessary to find a way to get chlorine in the nucleus. The difficulty of putting a single chlorine atom in the correct position has been pointed out (JA 13-16 and pp. 12-13 *supra*).

Most importantly, however, although imipramine has anti-depressant properties, the superiority of the claimed compound in this field was found by the District Court to be so large and far-reaching as to amount to a new result (Finding of Fact 10, JA 249).

The basis for this finding was the testimony of Dr. Garonne and Professor Deniker.

Dr. Gaston Garonne is a physician, in charge of the Psychiatric Polyclinic at the University of Geneva. During the prosecution of this application in the Patent Office an affidavit by Dr. Garonne (JA 96-107) was made of record showing the results of using the claimed compound on twenty-three patients. In this affidavit Dr. Garonne stated that he found the claimed compound to be an effective anti-depressant. Specifically he stated (JA 106-107):

"The average dose per day of active ingredient given was 50 to 75 mg. The period of latency between the outset of the treatment and the first effect is short, usually between 4 and 6 days, a positive response manifesting itself as early as on the 2nd day of treatment. The compound is of great interest to us. Its therapeutic effect manifests itself faster than that of any other known thymolepticum. Any side effects do not differ from those which can be observed under the same conditions as to the therapeutic effect with other commercial psychotropic drugs."

Called upon to testify at the second trial, Dr. Garonne affirmed the statements made in his affidavit (JA 194), adding only that he now considers chlorimipramine, the claimed compound, to have less side effects than other compounds. Furthermore, Dr. Garonne stated that he had now used the drug on about 100 additional patients with effects similar to those described in his affidavit.

Dr. Garonne further stated that he was familiar with imipramine (the compound of the Kuhn and Haefliger references) and that the speed of effect of chlorimipramine was about twice that of imipramine. He stated that the side effects of chlorimipramine are much less than those of imipramine. He further stated that in cases of severe depression where it is indispensable to obtain a rapid improvement, chlorimipramine may be used, while imipramine may not, without hospitalizing the patient.

Professor Pierre Deniker is also a doctor of medicine. He is Professor of Neuropsychiatry at the University of Paris. He testified (JA 207-216) that his research group had made a systematic study of some 150 patients to see whether chlorimipramine could be used to replace electroshock therapy in the treatment of severely depressed patients, where electroshock is currently the preferred treatment. His group found that this could indeed be done (JA 214). Professor Deniker stated that so far as he was aware no other drug could safely be used for this purpose; that if any were so used, the physician would be taking a grave risk of suicide (JA 209). He further stated that he was familiar with imipramine (the compound of the Kuhn article) and that imipramine was not useful for this purpose (JA 210).

In addition to its outstanding value as a replacement for electroshock therapy in treating depression, Professor Deniker stated that chlorimipramine could be used in the treatment of apathetic schizophrenia (JA 211-212). Here it is possible to use imipramine, but only in combination with

tranquilizing drugs. Chlorimipramine, on the other hand, can be used without additional drugs and gives distinctly superior results.

Finally, Professor Deniker indicated that chlorimipramine was exceptionally useful in the treatment of neurotics who resist "enormously" both conventional chemotherapy and psychotherapy (JA 213).

Comparing the dosages, Professor Deniker confirmed Dr. Garonne's testimony that chlorimipramine is effective in slightly less than half the dosage of imipramine (JA 213).

Professor Deniker pointed out that in addition to the 150 patients which his group had studied intensively, chlorimipramine had been used over the past four years on several hundred patients at the University Clinic in Paris with remarkable results (JA 208).

From the testimony of Dr. Garonne and Professor Deniker it is clear that chlorimipramine, the compound claimed, is an anti-depressant of remarkable efficacy. It can be used in half the dosage of the only other anti-depressant disclosed in the cited prior art. It acts twice as fast and it can be used to replace electroshock treatment. This represents a far-reaching improvement indeed. Moreover, the prior art cited, rather than suggesting these improved properties, would lead away from them. While imipramine, having no chlorine in the molecule, is an anti-depressant, the compound of Schindler et al. with two chlorine atoms is useless as an anti-depressant. Thus, even if the *formula* of chlorimipramine were to have been postulated, the probability of that compound being an anti-depressant would have been considered remote because the Schindler patent compound, having two chlorine atoms per molecule, is not an anti-depressant and the normal inference would be that the introduction of chlorine suppresses anti-depressant properties.

Appellant attempts to discount the qualities of the claimed compound by quoting Kuhn to the effect that even cases resistant to shock therapy "may respond" to imipramine. This, of course, is not the same as stating, as Prof. Deniker did, that chlorimipramine can be used to *replace* electroshock treatment.

To draw a more familiar parallel, consider Mr. Jones and Mr. Smith each of whom have fevers, one caused by virus X, the other by virus Y. Antibiotic A may be used successfully to treat Jones and be entirely unsuccessful in treating Smith. Antibiotic B may be employed successfully in treating Smith. We do not think the Appellant would argue, however, that this shows B could be used to replace A in treating Jones. And Prof. Deniker definitely rejected the idea that imipramine could be used to replace electroshock (JA 209-210). It may be added, on this point, that while Appellant has been highly critical of the statements made by Appellees' witnesses, whom he had the opportunity to cross examine, because no clinical data were supplied, he urges that full faith be given to an obscure passage, unsupported by any data, in the summary of an article, whose author we have had no opportunity to confront.

Again, Appellant refers to the Kuhn article as stating that in schizophrenia without excitement imipramine "may work well". The fact that imipramine and other antidepressants are useful for such patients was pointed out by Professor Deniker (JA 212) but he made the point that with these other drugs it is necessary to use tranquilizers to avoid "a cycle of agitations and a crisis of delusions". With chlorimipramine, on the other hand, additional drugs are unnecessary.

Appellant's Brief (p. 22) states the proposition that a chemical compound is not patentable over a chemically closely related prior art compound, "especially in the absence of convincing and probative evidence demonstrating

a completely unexpected result." This proposition is Appellant's own creation. While the cases cited by Appellant in support thereof involved instances where compounds were held unpatentable over closely related known compounds, most have little bearing on the present case.

In *In re Herr*, 50 CCPA 705, 304 F 2d 907 (1962), evidence of androgenic activity in the claimed compound was held not to establish patentability because it was not disclosed in the specification. In a continuation-in-part application which *did* contain the proper disclosure, the same claims were allowed (*In re Herr*, 54 CCPA —, 377 F 2d 610 [1967]).

In *In re Druey*, 50 CCPA 1538, 319 F 2d 237 (1963), the claim was to an intermediate useful in making a sulfa-drug. Claims were obtained on the drug itself because of its advantage over closely related compounds, but this was held not to make the intermediate patentable. *In re Surrey, et al.*, 50 CCPA 1336, 319 F 2d 233 (1963), again involved an intermediate which was held unpatentable, on reasoning analogous to that used in *Druey*.

In re Zickendraht, et al., 50 CCPA 1529, 319 F 2d 225 (1963), was a double patenting case where there was no material difference in properties between two chemically similar compounds. In *In re Lohr, et al.*, 50 CCPA 1274, 317 F 2d 388 (1963), there was no clear showing of superiority, one of the claimed compounds being exactly equal in performance to a prior art compound.

In *In re Riden*, 50 CCPA 1411, 318 F 2d 761 (1963), the compound claimed was an insecticide. It contained two chlorine atoms. The prior art showed a similar compound but with three chlorine atoms. This was also useful as an insecticide. There was no clear qualitative difference between the compounds, the application merely stating that the two chlorine compound was "preferred". The Court held that one would expect the properties of the two and three chlorine compounds to be about the same, and in the absence of a showing that they were not, held the two chlo-

rine compound unpatentable. If this case has any application to the present situation, it is to suggest that the art would expect the two chlorine compound of Schindler et al. and the compound claimed to have similar properties. Applicant's discovery that the claimed compound is an effective anti-depressant is, therefore, contrary to what would have been expected, using the reasoning of *Riden*.

One can draw endless analogies from cases such as those referred to, but in the end the basic inquiry must always be was the compound, including its properties, obvious from the art of record. The naked formula of claim 8, as we have shown, was no more obvious from the cited art than thousands of other related compounds. On the other hand the record establishes the superior anti-depressant properties of the claimed compound over the only prior compound shown to have any anti-depressant properties, and that this superior efficacy was by no means obvious.

IV. Appellant's Attack on the District Court's Findings is Unconvincing.

A. Any Presumption of Correctness Normally Applicable to the Holding of the Patent Office Is of Little Effect at This Time.

At page 8 of his Brief, Appellant argues that a presumption of correctness attaches to a holding of the Patent Office on the issue of obviousness. The authority cited is *Hays et al. v. Brenner*, 123 App. D. C. 96, 357 F 2d 287 (1966). There is no quarrel with the proposition as a general statement of the law.* However, any such presumption is more than outweighed by the fact that here a large number of the claims presented in the Patent Office were dropped before the District Court, by the extensive

* In *Hays*, obviousness was conceded and the issue was whether a terminal disclaimer would avoid "double patenting". This clearly is quite different from the issues here.

testimony presented in the District Court *Stradar v. Watson*, 100 App. D. C. 289, 244 F 2d 737 [1957]) and by the fact that the District Court, with the opportunity to hear the testimony and observe the witnesses, found for Appellees.

Moreover, the Haefliger and Kuhn references, upon which Appellant now chiefly relies, were not cited in the Patent Office proceedings.

B. The District Court's Decision Was Not Based "Exclusively" on the New Evidence Adduced at the Second Trial.

Throughout his Brief, Appellant has repeatedly stated that the District Court's Decision was based exclusively on the evidence adduced at the second trial. This is incorrect. The Court considered all the evidence and made that fact very clear to counsel for Appellant. On February 2, 1967, Appellant submitted two proposed Findings of Fact in addition to those proposed by Appellee. These proposed Findings read as follows:

"1. The evidence before the Patent Office would indicate that the compound of claim 8 was obvious to one of ordinary skill in the art from the teachings of the prior art.

"2. The further evidence introduced at the first trial leaves a doubt as to whether it is sufficient to justify the conclusion that the compound of claim 8 has effective anti-depressant properties."

The District Court, at the hearing held February 8, 1967, specifically refused to make Finding 1 above. As to Finding 2, the record is especially instructive (JA 244):

"The Court: Now, as to No. 2, No. 2 is completely contrary to what I deemed the evidence justifies.

"Mr. Armore: No. 2 refers only to the evidence in the first trial, and your Honor said in your opinion . . .

"The Court: *I have treated all the evidence as one.* I am not going to make those findings. I would be just stultifying my own decision if I did." (Emphasis added.)

Moreover, at page 9 of his Brief, in quoting the District Court on the efficacy of the evidence produced at the first trial, Appellant has chosen to omit a highly significant passage. The complete sentence reads as follows (JA 235):

"The Court has doubt whether that evidence, too, is sufficient to justify the conclusion of efficacy of the medicine, *but the sufficiency vel non of that particular evidence need not be determined* because at this hearing further evidence was introduced which the Court considers highly impressive". (Emphasis added.)

Thus, the District Court specifically pointed out (a) that it considered all the evidence, and (b) that it did *not* find the evidence introduced at the first trial insufficient.

Of course, the Haefliger and Kuhn references were newly presented at the second trial. Hence, as to them, the Court perforce relied exclusively on the testimony at the second trial.

C. The Testimony of Dr. Garrone and Professor Deniker Amply Supports the District Court's Findings of Fact.

The District Court, in Findings 8, 9 and 10 found that the claimed compound was being used to treat mental depression with a high degree of success, that it was so far superior to the compound of Haefliger and Kuhn that it could be used to supplant electro-shock treatment and that its efficacy was so large and far-reaching as to amount to a new result. As we have noted, these findings should not be overturned unless "clearly erroneous." So far as they pertain to the compound of Haefliger and Kuhn, the Court's findings were based chiefly on the testimony of Drs. Garrone and Deniker.

The Appellant's case is almost entirely on an attack on the Garrone and Deniker testimony. Appellant does not question that if Findings of Fact 8 to 10 are justified by the evidence, the ultimate finding of unobviousness is warranted. Moreover, he does not question that if the testimony of Drs. Garrone and Deniker is taken at face value, Findings 8 to 10 are justified. Essentially, therefore, Appellant's attack is on the *credibility* of Drs. Garrone and Deniker. Of course, the trial court's opportunity to observe their conduct, expression, bearing, and attitude made it particularly well equipped to judge their credibility, (*United States v. Yellow Cab Co.*, 338 US 338, 341 (1949); *United States v. Aluminum Co. of America*, 148 F 2d 416, 433, 2 Cir. [1945]) and the "clearly erroneous" requirement of Rule 52(a) is especially applicable.

D. Evidence of Comparative Results Was Produced.

The first attack on the testimony of Drs. Garrone and Deniker is that it was not based on "comparative tests." It is, of course, true that no formal series of comparative tests were conducted by these witnesses; indeed, as to the compound imipramine (Haefliger and Kuhn), Appellant could hardly have expected comparative test results to have been produced in the six days between his notice that the Haefliger and Kuhn references would be relied on, and the trial. In fact, however, both witnesses testified that they had had experience with imipramine as well as with chlorimipramine and then enumerated the advantages of chlorimipramine: half the dosage, twice the speed and the ability to replace electroshock.

As to the dichloro compound of Schindler et al., comparative tests on animals and on human patients *were* performed by Dr. Sigg and by Dr. Pöldinger. The results are in the record (JA 53-57, 63-68, 94). The dichloro compound has no anti-depressant effect.

The leading case cited by the Appellant, *Blanchard v. Ooms*, 80 App. D.C. 400, 153 F 2d 651 (1945), on the neces-

sity for comparative evidence is not applicable here. In that case and in the other cases cited to this point no evidence of superior performance was introduced. Here, however, there was testimony of highly skilled professional people to the superiority of the claimed compound, and the trial court found this testimony highly impressive.

E. The Testimony of Superior Results Was Clear and Positive.

On page 13 of his Brief, Appellant attacks the Deniker and Garrone testimony, apparently as being indefinite. However, it was not indefinite. Dr. Garrone gave precise dosages for imipramine and chlorimipramine (JA 196) which was supported by Professor Deniker (JA 213). Dr. Garrone stated that the speed of effect of chlorimipramine is about twice that of imipramine (JA 196). Professor Deniker (JA 214) definitely stated that the results of his study established that chlorimipramine was able to replace electroshock treatment. These are positive and definite statements, not contradicted by anything in the record.

The cases cited by Appellant in this section of his Brief are again not apposite. All of those cases involved decisions of the District Court adverse to the inventor which this Court felt it could not say were "clearly erroneous." Moreover, all involved instances where there was a serious question of novelty. In *Martin v. Watson*, 103 App. D.C. 106, 255 F 2d 184 (1958) the process claimed centered around a critical gas injection pressure to recover oil from sands. The Court noted (F 2d p. 185) that this very pressure was contemplated by a prior patent. In *Darison v. Watson*, 109 App. D.C. 296, 287 F 2d 150 (1961), the claims involved applying an old testing technique to milk. Broad claims were denied, but specific claims applicable only to milk were allowed. In *Reinauer v. Ladd*, 110 App. D.C. 300, 293 F 2d 139 (1961), the subject matter involved cleaning air filters, and it appeared that the elements relied upon to distinguish over the prior art were inherently pres-

ent in it. (Cf. F 2d p. 140.) In *Pollack v. Ladd*, 120 App. D.C. 318, 346 F 2d 799 (1965), this Court agreed with the District Court that "each of the claims was directly readable upon prior art."

Under the circumstances obtaining in these cases, since there was a lack of novelty, no amount of commercial success could result in patentability. Here, however, there is no question of novelty, and the District Court having had the opportunity to hear and observe the witnesses, found that the differences between the prior art and the claimed compound were so great as to amount to a new result. There was no such finding in the cited cases.

F. The Submission of Additional Raw Clinical Data Was Unnecessary.

On pages 13 to 21 of his Brief the Commissioner argues that the District Court erred in considering the Garrone and Deniker testimony because clinical records supporting the testimony were not put into evidence. Absent such raw data, Appellant argues, the Garrone and Deniker testimony amounts to no more than "unsupported conclusions or opinions."

This point was raised by the Appellant in his closing argument before the District Court (JA 228). The Court pointed out that although the absence of raw data from the record might be weighed on the probative value of the testimony, it did not make the testimony objectionable.

Before considering the probative value of the testimony, it is important to bear in mind the points to which the Garrone and Deniker testimony was directed. These were:

- (a) That chlorimipramine is useful as an anti-depressant, and
- (b) That chlorimipramine has advantages over the known compound imipramine.

The usefulness of the claimed compound cannot seriously be questioned. There is ample evidence, including specific clinical data, of its usefulness in the Pöldinger and Garrone affidavits (JA 94, 96-107), and the Pöldinger testimony (JA 61-75) as well as the Garrone and Deniker testimony. It would add nothing to have introduced masses of additional data on this point.

As to the advantages of chlorimipramine over imipramine, if the requirements argued for by Appellant were to be met, the results of systematic comparative tests would be required. These obviously could not have been collected in the six days between the Appellant's notice of his intent to rely on that prior art compound and the trial.

The fact is, however, that both Dr. Garrone and Dr. Deniker testified that they had had experience with both drugs and specified definite advantages of chlorimipramine over imipramine. They did not merely say "it's better" or "it acts faster" or "you don't have to give as much". They cited comparative dosages, relative latency periods and the fact, based on a clinical study of 150 severely depressed patients, that chlorimipramine could be used to replace ECT.

G. The Garrone Affidavit is Entirely Credible.

In his argument (Brief pp. 13-15), Appellant attacks the Garrone affidavit (JA 99-106) as containing "gross exaggerations", in respect to its conclusion on the period of latency. A study of the affidavit suggests, however, that Appellant's position is due rather to careless reading, than to any defects in the affidavit.

The period of latency referred to in the affidavit (JA 107) is the period between "the outset of the treatment and the first effect."* The affidavit says that this latency

* This "period of latency" is different from that referred to in the Garrone testimony (JA 196) which extends from the beginning of the treatment to the clinical cure.

period is short, usually 4 to 6 days. Appellant says this statement is unsupported by the data given in the affidavit. However, an inspection of the affidavit shows that of the 23 patients referred to in the affidavit, in sixteen the first effects were noted six days or less after treatment began, which is wholly consistent with the average of 4 to 6 days.

In fact, Appellant's analysis of the data given in the Garrone affidavit is itself tainted with exaggeration.

The affidavit describes the effect of the drug on 23 patients. But in tabulating the periods of latency from the affidavit (p. 14 of Appellant's Brief), Appellant has referred to a total of 37 patients!

Again, Appellant's Brief states (p. 14):

"It is also evident that there is no factual data to support Dr. Garrone's conclusion a positive response manifesting itself as early as on the 2nd day of treatment."

It is also evident that there is no factual data to support Dr. Garrone's conclusion

a positive response manifesting itself as early as on the 2nd day of treatment."

However, in Case 16 (JA 103) the "Effect of latency" is given as 2 days.

We may surely be forgiven for wondering, in the light of Appellant's mis-reading of the Garrone affidavit, what useful purpose would have been served in furnishing the additional raw data which he now demands.

H. The Garrone and Deniker Testimony Was Based on Facts and Experience Made of Record.

We do not question the general rule that the factual basis of opinion testimony must be disclosed to the extent necessary to show that the testimony is based on facts,

not on mere conjecture or guess work. To the extent that the Garrone and Deinker testimony was opinion, the factual basis for the opinion was clearly set forth. Drs. Garrone and Deniker stated that they had personally treated 123 and 150 patients with the new compound and that it was on this basis that their opinions were rendered. Data on 23 of Dr. Garrone's patients was presented (JA 99-106).

In any case, of course, the adequacy of the factual support affects the weight of the testimony, rather than its competency, as is brought out in the cases cited by the Appellant.

In *Balaban and Katz Corp. v. Commissioner of Internal Revenue*, 30 F 2d 807, 7 Cir. (1929), relied upon by Appellant, the question involved the period of obsolescence of a motion picture theatre. The obsolescence contemplated (it had not yet occurred) was that to be expected from advances in the art of designing theatres. Expert witnesses testified on the period of obsolescence but it was clear that the witnesses had *no* factual knowledge upon which to base their opinion. Even so, the Court found, not that this evidence *had* to be disregarded, but that it was *within the province of the Board of Tax Appeals to disregard it*.

In *Vincennes Water Supply Co. v. Public Service Commission of Indiana*, 34 F 2d 5, 7 Cir. (1939), an expert witness testifying to the value of a water supply system, never inspected much of the equipment and his opinion was therefore given little weight.

In *W. Horace Williams Co. v. Serpas*, 261 F 2d 857, 5 Cir. (1959), also cited by Appellant, there was conflicting testimony as to the extent of Plaintiff's injury. The lower Court adopted the views of Plaintiff's physician although his testimony was based primarily on a case history, not in evidence, rather than on first-hand physical examination. The Court of Appeals found that the case history appeared

to have been consistent with other testimony in the case and that while the lower Court *might* have found to the contrary, they were justified in finding for the Plaintiff.

In the present case, the testimony of Drs. Garrone and Deniker was based on actual observation of large numbers of patients. It was not based on conjecture and it was within the province of the District Court to believe that testimony.

I. The Jarvik Article Is Not in Evidence and Should Not Be Taken Into Account.

Appellant in his Brief, pp. 17-19, quotes at length from an article by one Murray E. Jarvik on the use of controls in testing psycho-pharmaceuticals. The identity of the author or his qualifications are not given, nor has there been any opportunity for cross-examination, or for the introduction of interpretative or contradictory testimony. The quotation should therefore be disregarded.*

In any case, the point discussed by Jarvik, the role of the so-called "placebo effect" in the testing of psycho-pharmaceuticals, was effectively dealt with by the witnesses. As Dr. Garrone pointed out (JA 201), it is characteristic of depressed patients not to believe in the effectiveness of a drug. Dr. Deniker (JA 215) stated that for ethical and medical reasons, he would not give an inert substance to depressed patients. And note the testimony of Dr. Pöldinger (JA 70-71).

Mental depression has been described by one authority as "the only emotional disorder with a fatality rate."**

* The situation is not like that in *Baenitz v. Ladd*, 124 App. D.C. 237, 363 F. 2d 969, 148 USPQ 187 (1966), where a literature citation was relied upon only to establish the existence of a particular chemical solution. Here the reference is cited on what is essentially a matter of professional judgment or opinion.

** Hollister, *Clinical Pharmacology and Therapeutics*, 6, 556 (1965).

Suicide is an ever present danger. For a physician to administer what he *knows* is not an effective medicine to a patient in imminent danger of committing suicide, would, for many physicians at least, be a breach of ethics. If the drug in question were advocated as useful against pneumonia, we do not suppose Appellant would seriously urge administering sugar pills to patients in danger of death from that disease in order to preserve the academic purity of an experiment. Yet this, in essence, is what the Appellant is advocating here.

The law does not require more than what is reasonable under the circumstances. Appellant's demands would require human patients to be treated like laboratory animals. This is not within the bounds of reason.

J. The Food and Drug Laws Have No Bearing on the Present Case and the Attempt by the Commissioner to Apply the Requirements of the Food, Drug and Cosmetic Act to the Present Patent Application Is Arbitrary.

Appellant attempts to assert that the FDA requirements for the marketing of a new drug should be imposed on inventors seeking to patent a new drug. This position has no foundation in statute or precedent. The purposes of the food and drug laws and the patent laws are different. The patent laws are aimed at the advancement of the useful arts. In meeting that objective, one desideratum is the early publication and disclosure of inventions. The food and drug laws, on the other hand, are primarily concerned with protecting the consumer. In line with this objective, the tests required for FDA approval involve far longer times than would be desirable in the Patent Office. If every pharmaceutical patent application were required to be supported by FDA type data, virtually all such applications would be finally rejected long before the data became available. This is particularly true with inventions made abroad, where patent applications must be filed

immediately, since the patent goes to the first-to-file, not to the first inventor.

There is nothing whatever in the Patent Laws or Patent Office Rules of Practice which lay down any such requirement, nor is such requirement derivable from the case law. *In re Hartop*, 50 CCPA 780, 311 F 2d 249, 135 USPQ 419 (CCPA, 1962).

The section of the Food Drug and Cosmetic Act (21 USC 355), quoted by Appellant, is explicit as to the standards to be met before new drugs may be introduced into commerce. The Secretary of Health, Education and Welfare has promulgated detailed regulations setting out the nature of the data to be supplied to obtain new drug approval (New Drug Regulations, Section 130.4).

The Patent Act, on the other hand (35 USC), sets out no specific requirements for the type of data to be supplied in establishing patentability. The Commissioner of Patents has promulgated Rules of Practice (37 C.F.R.) governing practice before the Patent Office. There is nothing in these rules which would require explicitly or by implication the kind of data Appellant now demands.

Appellees respectfully submit that it is clearly arbitrary, in the absence of any regulation even remotely resembling those published under the Food, Drug and Cosmetic Act, for Appellant now to insist that data of this nature is necessary to establish patentability.

As a matter of fact, however, the standards set down in the quoted portion of 21 USC 355 have been substantially met by Appellees. The psychiatrists who testified were amply qualified for their task, and controls were employed in the sense that the history of the patients was known and their progress after administration of the drug was observed (JA 71-73, 200-202, 215). That the type of controls advocated by the Patent Office was not used or that raw data was not submitted, does not alter the fact

that the drug has been investigated by qualified experts who fairly and responsibly concluded that the drug has the effect it is represented to have.

V. Conclusion

The claimed compound is novel and useful in the treatment of mental depression. While it is chemically related to known compounds, it is no more closely related than thousands of other compounds and its superiority in the treatment of mental depression, with respect to the only prior compound shown to have anti-depressant properties, is great and far-reaching. The finding of the District Court that the compound was unobvious is clearly supported by the Record and should be affirmed.

Respectfully submitted,

WILLIAM A. SMITH, JR.,
Attorney for Appellees.

CASPAR C. SCHNEIDER, JR.
DAVIS, HOXIE, FAITHFULL & HAPGOOD,
KARL F. JORDA,
Of Counsel.

